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Cost-Effectiveness Analyses of Anti-Resorptive Agents for Management of Glucocorticoid-Induced Osteoporosis and Fractures: Empirical Estimates from the 1996-2004 MEPS Data and Longitudinal Projection from Markov Modeling

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To my dear wife, Chia-Hui, my parents and in-laws

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Cost-Effectiveness Analyses of Anti-Resorptive Agents for Management of Glucocorticoid-Induced Osteoporosis and Fractures: Empirical Estimates from the 1996-2004 MEPS Data and Longitudinal Projection from Markov Modeling

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Long-term glucocorticoid use leads to glucocorticoid-induced osteoporosis (GIOP) and fractures which require proper management. Little is known about the "real-world," long-term costs and effectiveness of anti-osteoporotic treatments. A retrospective analysis of data from the 1996-2004 Medical Expenditure Panel Survey was conducted to evaluate the "real-world" outcomes. Markov modeling with Monte Carlo simulations was used to yield long-term estimates of these outcomes.

A total of 5,461 subjects met the study criteria for long-term glucocorticoid users (LTGS, average prednisone-equivalent dose=11.0 mg/day, average length=237 days), which represents 2.3% of the non-institutional U.S. population. The study subjects tended to be middle-aged (49.7 years old), female (61.4%) and white (86.2%). Overall,

22.4% of LTGS users reported use of any anti-osteoporotic agent. Hormone replacement therapy (HRT) was the most frequently used in women followed by bisphosphonates, while bisphosphonates and calcitonin were used by men. Analyses of variance indicated some significant differences in characteristics of LTGS users among treatment groups which suggest a selection bias. Female LTGS users had higher prevalence rates (6.8%) of osteoporosis than males (1.0%), but the prevalence rates of osteoporotic fractures were similar (3.0%). The logistic regression analyses indicated that the use of oral glucocorticoid tablets does not significantly change the odds of osteoporotic fractures in study subjects (relative risk (RR)=1.146, 95% confidence interval (CI) 0.901-1.458 for subjects in the WELL state; RR=0.55, 95% CI 0.188-1.621 for subjects in the GIOP state; RR=1.241, 95% CI 0.532-2.893 for subjects in the GIFX state).

The estimated 10-year and lifetime incremental cost per osteoporotic fracture avoided are $27,253-$35,692 (10-year) and $84,942-$91,075 (lifetime) in hypothetical female glucocorticoid users. HRT is the most cost-effective option for hypothetical females except that calcitonin is preferred for 65-year-old females receiving lifetime treatments. When HRT is excluded, calcitonin is the next most cost-effective option except that raloxifene is preferred for 30- and 50-year-old females receiving 10-year treatments. Calcitonin is the most cost-effective option for male glucocorticoid users. Bisphosphonates are less cost-effective which may be due to selection bias. Anti-osteoporotic treatments are recommended for all long-term glucocorticoid users, but the preferred option depends on gender, age, length of treatments and budgets.

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CHAPTER ONE-OVERVIEW

1.1 INTRODUCTION

Because of significant anti-inflammatory and immunosuppressive properties, glucocorticoid steroids (GS) are widely used to treat various conditions (such as pulmonary disorders, rheumatic diseases, skin problems and organ transplantations), many of which are chronic and require prolonged therapy. Patients with these chronic conditions are frequently prescribed glucocorticoid steroids for a long period of time. An important complication of long-term glucocorticoid treatment is the loss of bone mass.[1] If this condition is not prevented or treated properly, long-term glucocorticoid users may develop glucocorticoid-induced osteoporosis (GIOP) with increased risks of osteoporotic fractures and mortality.[2] Because some osteoporotic fractures are strongly associated with permanent disability and premature death, proper interventions are highly recommended for those receiving extended glucocorticoid therapy to avoid severe consequences.

Currently available interventions include: (1) lifestyle modification (e.g., smoking cessation, reduced consumption of alcohol, sufficient nutrition for calcium from dairy products and other food, increased physical/weight-bearing exercise); (2) over-the-counter (OTC) medications (calcium and vitamin D supplements); and (3) prescribed medications (such as anti-resorptive agents and anabolic agents).[3] Prescribed

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1 Cushing, H. W. (1932). The basophile adenomas of the pituitary body and their clinical manifestations. *Bulletin of the Johns Hopkins Hospital* 50: 137-195.

2 van Staa, T. P. *et al*. (2001). Public health impact of adverse bone effects of oral corticosteroids. *British Journal of Clinical Pharmacology* 51(6): 601-607.

3 National Osteoporosis Foundation. (2003). Physician's guide to prevent and treatment of osteoporosis. National Osteoporosis Foundation; Washington, D.C. 37 pages.

medications are the main focus of this study. These medications have demonstrated increased bone mineral density (BMD) and a decreased risk of osteoporotic fractures in randomized clinical trials (RCTs).[4, 5] The findings of RCTs for calcium/vitamin D and prescribed medication will be discussed and summarized in Chapter Two. Brief highlights are as follows.

- **OTC medications**

In many osteoporosis studies, calcium/vitamin D supplements were used as a baseline treatment for all study groups. Because patients with bone loss are losing calcium, an intuitive approach is to provide calcium and vitamin D supplements. There are many subtypes of vitamin D, among which vitamin D_3 and its derivatives (e.g., alfacalcidol, calcitriol, cholescalciferol) have received much attention in studies related to glucocorticoid-induced osteoporosis.[6, 7, 8, 9, 10] Combined use of calcium and vitamin D supplements has demonstrated evidence of slowing the rate of bone loss, but not to

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4 American College of Rheumatology. (1996). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on osteoporosis guidelines. *Arthritis and Rheumatism* 39(11): 1791-1801.

5 American College of Rheumatology. (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocorticoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

6 Ringe, J. D. *et al*. (2004). Superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis. *Rheumatology International* 24(2): 63-70.

7 Barthel, H. R. & Vieth, R. (2004). Lack of generalizable evidence of the superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis: comment on the article by Ringe *et al*. *Rheumatology International* 24(4): 250-251.

8 Gram, J. *et al*. (1998). Effects of short-term treatment with prednisolone and calcitriol on bone and mineral metabolism in normal men. *Bone* 23(3): 297-302.

9 McDonald, C. F. *et al*. (2006). Calcitriol does not prevent bone loss in patients with asthma receiving corticosteroid therapy: a double-blind placebo-controlled trial. *Osteoporosis international* 17(10): 1546-1551.

10 de Nijs, R. N. J. *et al*. (2004). Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D_3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. *Osteoporosis International* 15(8): 589-602.

reduce risks of some osteoporotic fractures.[11, 12] A daily supplementation of 1,500 milligrams (mg) of calcium and 400 International Units (IU) of vitamin D is recommended for glucocorticoid-induced osteoporosis.[13]

- **Prescribed medications**

Anti-resorptive agents include bisphosphonates, agents for replacement of gonadal sex hormones, selective estrogen receptor modulators (SERMs) and calcitonin. Bisphosphonates (e.g., alendronate and risedronate) show significant efficacy regarding the prevention and the treatment of glucocorticoid-induced osteoporosis and postmenopausal osteoporosis.[14, 15, 16, 17] Bisphosphonates increase bone density at most vulnerable sites of bone and reduce risks of osteoporotic fractures, so they are usually the first choice for preventing and treating all types of osteoporosis. Hormone replacement therapy (HRT, e.g., estrogens and testosterone) shows a risk reduction of

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11 Meunier, P. J. (1999). Calcium, vitamin D and vitamin K in the prevention of fractures due to osteoporosis. *Osteoporosis International* 9(suppl. 1): S48-S52.

12 Porthouse, J. *et al*. (2005). Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *British Medical Journal* 330(7498): 1003-1008.

13 American College of Rheumatology. (1996). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on osteoporosis guidelines. *Arthritis and Rheumatism* 39(11): 1791-1801.

14 Saag, K. G. *et al*. (1998). Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *New England Journal of Medicine* 339(5): 292-299.

15 Adachi, J. D. *et al*. (2001). Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis and Rheumatism* 44(1): 202-211.

16 Lems, W. F. *et al.* (2006). Positive effect of alendronate on bone minieal density and makers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. *Osteoporosis International* 17: 716-723.

17 Reid, D. M. *et al*. (2000). Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. *Journal of Bone and Mineral Research* 15(6): 1006-1013.

osteoporotic fractures and was once widely used among postmenopausal women.[18] After the discovery of increased risks of cardiovascular diseases, thromboembolism and breast cancer since 2002, HRT is generally not recommended for osteoporosis anymore.[19, 20] Raloxifene which is the only SERM currently used for osteoporosis, decreases the risks of vertebral fractures and breast cancer, and could be used for osteoporosis in postmenopausal women.[21] Calcitonin, which is a peptide derived from salmon proteins, moderately increases the values of BMD, but does not significantly reduce the risk of vertebral fractures.[22] Although calcitonin shows relatively weak efficacy, it still serves as the second-line agent for osteoporosis because of its pain management potential with vertebral fractures.[23, 24] Calcitonin is also frequently used when a patient with osteoporosis has a contraindication with bisphosphonates.[25] Teriparatide, which is a human parathyroid segment (PTH 1-34), is an anabolic agent and is currently the only approved prescribed medicine which increases the process of bone formation.

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18 Geusens, P. (2000). Hormonal replacement therapy in the prevention and treatment of glucocorticoid-induced osteoporosis. *Clinical and Experimental Rheumatology* 18(suppl. 21): S57-S59.

19 Kleerekoper, M. (2002). Lessons from the skeleton: was the Women's Health Initiative (WHI) a primary prevention trial? *Osteoporosis International* 13(9): 685-687.

20 Majumdar, S. R. *et al*. (2004). Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *Journal of the American Medical Association* 292(16): 1983-1988.

21 Seeman, E. *et al*. (2006). Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporosis International* 17(2): 313-316.

22 Healey, J. H. *et al*. (1996). A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcified Tissue International* 58(2): 73-80.

23 Coyle, D. *et al*. (2001). Cost effectiveness of nasal calcitonin in postmenopausal women: use of Cochrane collaboration methods for meta-analysis within economic evaluation. *Pharmacoeconomics* 19(5): 565-575.

24 Knopp, J. *et al*. (2005). Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. *Osteoporosis International* 16(10): 1281-1290.

25 American College of Rheumatology (ACR) (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

Teriparatide has demonstrated risk reduction of both vertebral and non-vertebral fractures in two-year RCTs, [26] but the efficacy beyond two years is not established. Among all of these agents, alendronate (Fosamax®) and risedronate (Actonel®) are the only prescribed medicines which were approved by the U.S. Food and Drug Administration (FDA) for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). Nevertheless, other anti-osteoporotic agents which were approved for other types of osteoporosis may still be used clinically for glucocorticoid-induced osteoporosis.

- **Guidelines for Glucocorticoid-Induced Osteoporosis**

There are three types of osteoporosis. Postmenopausal osteoporosis (Type 1) is mostly due to hypogonadism. Senile osteoporosis (Type 2), associated with decreased bone formation, occurs with an increased age. Glucocorticoid-induced osteoporosis is the leading cause of secondary osteoporosis (Type 3), which refers to osteoporosis caused by or associated with diseases or pharmacotherapy. The pathogenic mechanism of glucocorticoid-induced osteoporosis should not be confused with those of other types of osteoporosis. [27] An agent that is good for treating one type of osteoporosis may not have the same efficacy for treating glucocorticoid-induced osteoporosis.

In the past decade, glucocorticoid-induced osteoporosis has been receiving more attention globally. Since 1996, many guidelines or consensus reports have been developed for glucocorticoid-induced osteoporosis. The American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis and the

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26 Lane, N. E. *et al*. (2000). Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. *Journal of Bone and Mineral Research* 15(5): 944-951.

27 Canalis, E. (2003). Mechanisms of glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 15(4): 454-457.

American Medical Association (AMA) provided recommendations to physicians in the United States.[28, 29, 30] It is suggested that patients receiving long-term glucocorticoid therapy (≧ 5 mg/day, ≧ three months) modify lifestyle, initiate weight-bearing physical exercise, measure bone mineral density (BMD) at lumbar spine and/or hip every one year or as frequent as six months, and should be provided supplementation with calcium and vitamin D (plain or activated form) at a dosage of 800 IU/day. Bisphosphonates should be prescribed in all men and postmenopausal women when BMD is below normal (e.g., T-score < -1), and calcitonin should be considered as a second-line agent if patients do not tolerate or have contraindication to bisphosphonate therapy. However, it was emphasized that these recommendations are not mandated, and that final decisions on management of glucocorticoid-induced osteoporosis should consider patients' individual needs.

A similar guideline published in 2003 was specifically designed for American veterans.[31] Weight-bearing exercise, prevention of falls and calcium plus vitamin D therapy are recommended to all patients receiving glucocorticoid therapy for at least three months, followed by careful monitoring of urinary calcium. Bisphosphonates are recommended to patients with prior fractures and to those receiving ≧ 5 mg/day of prednisone with abnormal BMD. Hormone replacement therapy or raloxifene is an

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28 American College of Rheumatology (1996). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on osteoporosis guidelines. *Arthritis and Rheumatism* 39(11): 1791-1801.

29 American College of Rheumatology (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

30 American Medical Association (1999). Managing osteoporosis. Part 2: glucocorticoid-induced osteoporosis-AMA continuing medical education program for primary care physicians; 23 pages.

31 Adler, R. A. & Hochberg, M. C. (2003). Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the Department of Veterans Affairs. *Archives of Internal Medicine* 163(21): 2619-2624.

alternative for postmenopausal women. If gonadal status is low, estrogen or testosterone replacement therapy is an alternative for premenopausal women and men.

In 1998, a management algorithm for glucocorticoid-induced osteoporosis was published by a consensus group in the United Kingdom.[32] This UK consensus report suggested that oral glucocorticoid users receiving 7.5 mg/day for at least six months incorporate lifestyle modifications, take calcium and vitamin D supplementation if deficient in the normal diet, discuss glucocorticoid regimens and alternative with physicians, and measure BMD if available. Diagnostic tests and assessment of hypogonadism should be performed if an abnormal BMD (T-score < -1.5) is found. Hormone replacement therapy (HRT) should be used for all postmenopausal women, and bisphosphonates are the first-line treatment in men and for women who are unwilling to take HRT. Assessment of response to treatments should be followed after one year, and treatments should be adjusted accordingly. It should be noted that the management algorithm has not been evaluated by formal economic modeling nor has the diagnostic assessment, so future pharmacoeconomic research is needed.

Another consensus report on prevention of glucocorticoid-induced osteoporosis was provided by the Dutch Society for Rheumatology..[33] The main difference in diagnostic and therapeutic steps from U.S. and U.K. recommendations is that bisphosphonates should be provided "immediately in patients at high risk" (e.g., all patient receiving $\geqq$ 15 mg/day of glucocorticoids or prevalence fracture or postmenopausal women and elderly men receciving $\geqq$ 7.5 mg of glucocorticoids). In 2004, the Japanese Society for Bone and Mineral Reseach also proposed a guideline for

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32 Eastell, R. *et al.* (1998). A UK consensus group on management of glucocorticoid-induced osteoporosis: an update. *Journal of Internal Medicine* 244(4): 271-292.

33 Geusens, P. *et al*. (2004). Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. *Annals of the Rheumatic Diseases* 63(3): 324-325.

glucocorticoid-induced osteoporosis based on research conducted by subcommittee members.[34] Bisphosphonates (e.g., etidronate, alendronate and risedronate) are recommended as first-line treatment. Specially, vitamin D_3 and vitamin K_2 are recommended as the second-line treatment because the latter was found to have a preventive effect on fractures in a longitudinal study in Japan.[35]

Recently, a consensus guideline on prevention and treatment of glucocorticoid-induced osteoporosis was reported by the Belgian Bone Club.[36] It emphasized that all glucocorticoid users are threatened with osteoporosis, so all postmenopausal women as well as men and premenopausal women who expect to receive 7.5 mg/day of prednisolone for at least three months should attempt to prevent glucocorticoid-induced osteoporosis. Non-pharmacological interventions are recommended to all patients. Supplementation with 500-1,000 mg of calcium and 800-1,000 IU of vitamin D is the first-line treatment. Bisphosphonates could be used as the second-line treatment to all patients at risk. Other alternatives include hormone replacement therapy which could be used in young postmenopausal women on glucocorticoid therapy and men with low androgen levels, and calcitonin which could be considered in postmenopausal women. No data were found to support the use of raloxifene and combination therapy other than calcium plus vitamin D in glucocorticoid users.

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34 Soen, S. & Tanaka, Y. (2005). Glucocorticoid-induced osteoporosis: skeletal manifestations of glucocorticoid use and 2004 Japanese Society for Bone and Mineral Research-proposed guidelines for its management. *Modern Rheumatology* 15(3): 163-168.

35 Tanaka, I. & Oshima, H. (2003). A longitudinal study of diagnosis and treatment for glucocorticoid-induced osteoporosis. *Osteoporosis Japan* 11: 11-14.

36 Devogelaer, J. P. *et al.* (2006). Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. *Osteoporosis International* 17(1): 8-19.

Many papers and reviews have also discussed the importance of the prevention and treatment of glucocorticoid-induced osteoporosis.[37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60] These articles provided an overview of

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37 Adachi, J. D. & Ioannidis, G. (2000). glucocorticoid-induced osteoporosis. *Drug Development Research* 49: 120-134.

38 Bijlsma, J. W. J. (1997). Prevention of glucocorticoid induced osteoporosis. *Annals of the Rheumatic Diseases* 56(9): 507-509.

39 Boulos, P. *et al*. (2000). Glucocorticoid-induced osteoporosis. *Current Rheumatology Reports* 2(1): 53-61.

40 Buckley, L. M. (1997). Importance of guidelines on glucocorticoid-induced osteoporosis: comment on the American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis and Rheumatism* 40(8): 1547.

41 Clowes, J. A. *et al*. (2001). Glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 13(4): 326-332.

42 Eggelmeijer, F. (1998). Prevention and treatment of glucocorticoid-induced osteoporosis. *Pharmacy World and Science* 20(5): 193-197.

43 Koval, P. G. *et al*. (2002). What are effective strategies for reducing the risk of steroid-induced osteoporosis? *Journal of Family Practice* 51(12): 1076.

44 Lane, N. E. *et al*. (1995). Prevention and management of glucocorticoid-induced osteoporosis. *Bulletin on the Rheumatic Diseases* 44(5): 1-4.

45 Lane, N. E. (2001). An update on glucocorticoid-induced osteoporosis. *Rheumatic Diseases Clinics of North America* 27(1): 235-253.

46 Lips, P. (1999). Prevention of corticosteroid induced osteoporosis: should be easier if doctors follow the recent guidelines. *British Medical Journal* 318(7195): 1366-1367.

47 Manelli, F. & Giustina, A. (2000). Glucocorticoid-induced osteoporosis. *Trends in Endocrinology and Metabolism* 11(3): 79-85.

48 Meunier, P. J. (1993). Is steroid-induced osteoporosis preventable? *New England Journal of Medicine* 328(24): 1781-1782.

49 Niewoehner, C. B. & Niewoehner, D. E. (1987). Steroid-induced osteoporosis. Are your asthmatic patients at risk? *Postgraduate Medicine* 105(3): 79-83.

50 O'Mahony, D. (1999). Prevention of corticosteroid-induced osteoporosis and fractures. *Journal of Clinical Pharmacy and Therapeutics* 24(2): 83-85.

51 Peat, I. D. *et al*. (1995). Steroid induced osteoporosis: an opportunity for prevention? *Annals of the Rheumatic Diseases* 54(1): 66-68.

52 Ramsey-Goldman, R. (2002). Missed opportunities in physician management of glucocorticoid-induced osteoporosis? *Arthritis and Rheumatism* 46(12): 3115-3120.

53 Reid, I. R. (1997). Preventing glucocorticoid-induced osteoporosis. *New England Journal of Medicine* 337(6): 419-421.

54 Ringe, J. D. (1989). Glucocorticoid-induced osteoporosis. *Clinical Rheumatology* 8(suppl. 2): 109-115.

55 Saag, K. G. (2003). Glucocorticoid-induced osteoporosis. *Endocrinology and Metabolism Clinics of North America* 32(1): 135-157.

glucocorticoid-induced osteoporosis. These papers also discuss some pharmaceutical options based on evidence of protective effects on bone loss and fractures in the literature. Bisphosphonates show promising protective effects on glucocorticoid-induced bone loss, but evidence of other pharmaceutical options do not support a similar degree of protective effects. More research is needed.

- Efficacy vs. Effectiveness

Most of the guidelines, concensus reports and papers which were mentioned previously were based on evidence from randomized controlled trials (RCTs) in the literature. In addition to gender and age, some common exclusion criteria of these RCTs are comorbidity, prior anti-osteoporotic treatments and use of glucocorticoid steroids, anticoagulants and anticonvulsants. However, research has discovered that a significantly large percentage (>80%) of patients who were diagnosed with osteoporosis and being considered for RCTs for osteoporosis were excluded as a result of exclusion criteria.[61] From the perspective of managed care, study results from RCTs (i.e., efficacy) may not be applicable to these patients who often consume the largest portion of medical sources and encounter significant amounts of direct medical costs. Additionally, the sample size in most RCTs is too small to yield enough statistical power

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56 Sambrook, P. N. (2005). How to prevent steroid induced osteoporosis. *Annals of the Rheumatic Diseases* 64(2): 176-178.

57 Tamura, Y. *et al*. (2004). Glucocorticoid-induced osteoporosis. *Biomedicine and Pharmacotherapy* 58(9): 500-504.

58 Tan, T. T. *et al*. (1997). Steroid-induced osteoporosis-a cause for concern? *Malaysian Journal of Pathology* 19(1): 27-33.

59 Weinstein, R. S. (2001). Glucocorticoid-induced osteoporosis. *Reviews in Endocrine and Metabolic Disorders* 2(1): 65-73.

60 Ziegler, R. & Kasperk, C. (1998). Glucocorticoid-induced osteoporosis: prevention and treatment. *Steroids* 63(5-6): 344-348.

61 Dowd, R. *et al.* (2000) Study subjects and ordinary patients. *Osteoporosis International* 11(6): 533-536.

for detection of significant differences in fracture rates between treatments.[62] Therefore, efficacy from RCTs should be interpreted with caution in managed care settings.

Effectiveness, on the other hand, reflects the "real-world" conditions and has received more and more attention from the perspective of managed care.[63] Effectiveness and "real-world" data can be obtained from existing databases and retrospective analyses.[64] Compared to RCTs, retrospective database analyses feature relatively inexpensive and assessable data, quick study results, more realistic time-frame, large sample sizes and inclusion of study subjects in multiple regions, health plans, treatment groups and physician specialties.[65, 66] However, retrospective database analyses also carry some limitations which include no control over variables of interest (such as calcium and vitamin D as over-the-counter medications), errors in data coding, problems of causal linkage and selection bias.[67, 68]

It has been estimated that less than one percent of the general population used glucocorticoid steroids for at least three months.[69, 70] The incidence of osteoporotic

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62 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

63 Arnold, R. G. *et al.* (1999). Panel 3: Methodological issues in conducting pharmacoeconomic evaluations-retrospective and claims database studies. *Value in Health* 2(2): 82-87.

64 Yood, R. A. *et al*. (2001). Prevention of glucocorticoid-induced osteoporosis. *Archive Internal Medicine* 161: 1322-1327.

65 Arnold, R. G. *et al.* (1999). Panel 3: Methodological issues in conducting pharmacoeconomic evaluations-retrospective and claims database studies. *Value in Health* 2(2): 82-87.

66 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

67 *Ibid.*

68 Motheral, B *et al.* (2003) A checklist for retrospective database studies-report of the ISPOR Task Force on retrospective databases. *Value in Health* 6(2): 90-97.

69 Gudbjornsson, B. *et al*. (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

70 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

fractures is generally too low to be detected in studies with a small sample size.[71] Research on glucocorticoid-induced osteoporosis should include study samples in thousands or tens of thousands in order to reach enough statistical power to detect significant differences in fracture rates between anti-osteoporotic treatments. Additionally, it has been noted that "fracture risk is not directly linked to BMD,"[72] which is often the primary outcome measured in most RCTs. A large database should include records for osteoporotic fractures, with the ability to link medical records to pharmacy data for retrospective analyses. Therefore, retrospective database analyses which yield costs and effectiveness data served as the best option for this study.

1.2 STUDY GOALS AND RATIONALE

This study aims to reach two goals. The first study goal is to raise awareness of glucocorticoid-induced bone loss and related fractures in the U.S. The study provides U.S.-based epidemiological estimates of osteoporosis and osteoporotic fractures. The second study goal is to aid decision-making on use of preventive anti-osteoporotic treatments for glucocorticoid users, and to suggest preferable options. This goal can be reached by providing "real-world" information on short-term and long-term costs and effectiveness of anti-osteoporotic treatments.

When patients take glucocorticoid medications for a prolonged period of time (e.g., at a daily dosage of more than 5 mg for more than three months), an important potential side effect is bone mass loss, which increases risks of (glucocorticoid-induced)

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71 Barrington, C. *et al.* (2006). Managing osteoporosis in a managed care population. *The American Journal of Managed Care* 12(7) S199-202.

72 *Ibid.*

osteoporosis and osteoporotic fractures.[73] If long-term glucocorticoid therapy is not discontinued and preventive interventions are not implemented, the risks of glucocorticoid-induced bone loss remains and could worsen as time passes. Glucocorticoid-induced bone loss should be properly managed.

Many anti-osteoporotic agents have shown protective efficacy on bone loss in RCTs, and two bisphosphonates have been specifically approved by the FDA for the prevention and treatment of glucocorticoid-induced osteoporosis. Studies and guidelines have suggested that long-term glucocorticoid users should receive preventive treatment for future bone loss and osteoporotic fractures.[74] However, a relatively large portion of these users still do not receive any anti-osteoporotic agents.[75, 76, 77, 78] Possible reasons may include, but are not limited to: (1) lack of significant awareness of risks of glucocorticoid-induced osteoporosis and osteoporotic fractures in the population at risk; (2) unconvincing evidence on long-term effectiveness of prevention or treatment of glucocorticoid-induced osteoporosis; and (3) concerns of unaffordable costs for anti-osteoporotic treatments.[79]

Providing appropriate information on threats of glucocorticoid-induced bone loss and fractures is one approach to raise awareness in glucocorticoid users. No

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73 American College of Rheumatology (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

74 See references 26 to 34.

75 Walsh, L. J. *et al*. (1996). Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *British Medical Journal* 313(7053): 344-346.

76 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

77 Aagaard, E. M. *et al*. (1999). Prevention of glucocorticoid-induced osteoporosis: provider practice at an urban county hospital. *American Journal of Medicine* 107(5): 456-460.

78 Hart, S. R. & Green, B. (2002). Osteoporosis prophylaxis during corticosteroid treatment: failure to prescribe. *Postgraduate Medical Journal* 78(918): 242-243.

79 Bijlsma, J. W. J. (1997). Prevention of glucocorticoid induced osteoporosis. *Annals of the Rheumatic Diseases* 56(9): 507-509.

information was found in the literature on prevalence and incidence of glucocorticoid-induced osteoporosis and related osteoporotic fractures in the U.S. population. This study estimates the average annual prevalence and incidence of glucocorticoid-induced osteoporosis and related osteoporotic fractures in the U.S. A cross-sectional analysis of nationally representative data provides current epidemiological estimates (i.e., prevalence and incidence of glucocorticoid-induced osteoporosis and osteoporotic fractures).

Patients, clinicians and payers may have difficulty in deciding whether it is better to spend money in advance to use anti-osteoporotic agents for the prevention of glucocorticoid-induced bone loss and osteoporotic fractures for long-term glucocorticoid users, or just treat glucocorticoid-induced osteoporosis and osteoporotic fractures when they occur. The simultaneous considerations of costs and effectiveness of anti-osteoporotic treatments are important in decisions regarding whether anti-osteoporosis medications should be recommended for long-term glucocorticoid users. An evaluation technique called cost-effectiveness analysis (CEA) could be used to facilitate the decisions on which approach is preferable by considering both the clinical (e.g., effectiveness of fracture prevention) and economic outcomes (e.g., direct medical costs) together. Glucocorticoid-induced osteoporosis occurs as early as three months after the initiation of glucocorticoid therapy, yet it progresses throughout an individual's lifetime. Therefore, both pieces of information regarding short-term and long-term clinical and economic evaluations of pharmacotherapy for the prevention and treatment of glucocorticoid-induced osteoporosis are equally important.

Information on long-term costs and effectiveness of anti-osteoporosis treatments is of specific interest for these decisions, but the literature is incomplete. Most cost-effectiveness studies targeting anti-osteoporotic agents in the literature were

designed for postmenopausal osteoporosis. Three studies which evaluated cost-effectiveness of anti-osteoporotic treatments for osteoporosis and osteoporotic fractures in glucocorticoid users were identified in the literature. However, the projected long-term estimates of cost-effectiveness of anti-osteoporotic agents were based on short-term efficacy data ("ideal" information) from the randomized clinical trials. It has been generally accepted that effectiveness data ("real-world" information) are more meaningful to the actual management of glucocorticoid-induced bone loss than efficacy data. Therefore, there is a need of "real-world" cost-effectiveness data of anti-osteoporotic treatments for long-term glucocorticoid users.

Long-term "real-world" cost-effectiveness information on anti-osteoporotic agents can be obtained from studies or databases that follow glucocorticoid users longitudinally. A longitudinal study on long-term cost-effectiveness of anti-osteoporotic treatments is currently not available in the literature, so long-term "real-world" cost-effectiveness estimates can be projected from short-term "real-world" data by using another technique called Markov modeling. To our knowledge, there is no study in the literature that has used actual expenditures as inputs in a Markov model to estimate the long-term cost-effectiveness of medications for glucocorticoid-induced osteoporosis.

This study generates both short-term and long-term estimates of average direct medical costs and effectiveness for prevention and treatment of osteoporosis and osteoporotic fractures in long-term glucocorticoid users. The short-term data should also reflect "real-world" situations as closely as possible, so this study uses data from the Medical Expenditure Panel Survey (MEPS), which provides nationally representative information on medical utilization and related expenses. The long-term estimates of

costs and effectiveness in glucocorticoid users who received any of anti-osteoporotic treatments will be compared with those who did not.

In short, this study provides information on: (1) descriptive statistics of glucocorticoid and anti-osteoporotic medication use, and characteristics of glucocorticoid users in the U.S.; (2) nationally representative estimates of prevalence and incidence of osteoporosis and osteoporotic fractures in glucocorticoid users; (3) nationally representative estimates of average medical costs for evaluation of osteoporosis, treatment of osteoporotic fractures and treatments by using anti-osteoporotic agents; (4) Markov models for estimations of long-term costs and effectiveness; (5) long-term estimates of costs and effectiveness of anti-osteoporotic treatment; (6) a summary and useful plots of cost-effectiveness and acceptability curves for comparisons among anti-osteoporotic options in glucocorticoid users. These study results should provide information which will facilitate clinical decisions for management of osteoporosis and osteoporotic fractures in glucocorticoid users in the U.S.

1.3 ABOUT THIS DISSERTATION

This dissertation consists of five chapters and appendices. This chapter provides a brief overview for this study. Chapter Two will elaborate on the existing evidence regarding glucocorticoid-induced osteoporosis and related osteoporotic fractures, and identify research questions from gaps or issues in the literature. Chapter Three will describe the study methodology and highlight some concepts, theories and issues regarding cost-effectiveness analysis and Markov modeling. Chapter Four will present study findings. Chapter Five will discuss study findings, and make recommendations for the management of osteoporotic fractures in glucocorticoid users. Appendices show

additional information on institutional review board's letter of approval, and additional tables of incidence rates of osteoporosis and osteoporotic fractures by gender, type of treatment and age groups. A bibliography for this study follows. A brief vita about the author is provided at the end of this dissertation.

1.4 SUMMARY OF CHAPTER ONE

Long-term glucocorticoid users have a significantly increased risk of developing glucocorticoid-induced osteoporosis and fractures, but interventions to prevent these conditions have received little attention. The lack of use of agents for proper management of glucocorticoid-induced osteoporosis and fractures may occur for many reasons, such as uncertainty of long-term effectiveness and financial burden of long-term costs of anti-osteoporotic treatments. Both short-term and long-term "real-world" cost-effectiveness information regarding expenditures and effectiveness associated with anti-osteoporotic agents will help decision-makers determine whether it is beneficial to use anti-osteoporotic agents in advance for the prevention of glucocorticoid-induced osteoporosis and related fractures. If the use of these preventive medications is warranted, the information may also help in choosing preferable options for long-term, high-risk glucocorticoid users.

CHAPTER TWO-LITERATURE REVIEW

This chapter reviews what is known about glucocorticoid-induced osteoporosis (GIOP) and osteoporotic fractures in the literature, identifies possible research questions, and describes study objectives and hypotheses. First, the possible pathogenic mechanism of glucocorticoid-induced osteoporosis is presented to help with the understanding of its clinical features and pharmacotherapeutic options. The epidemiology of glucocorticoid-induced osteoporosis is then reviewed to demonstrate the magnitude of this problem. Emphasis is placed on the clinical and economic outcomes of each therapeutic option. Gaps in the literature and possible research questions are then identified. Study objectives and hypotheses are listed at the end of this chapter.

First of all, osteoporosis needs to be clearly defined. Osteoporosis is "a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist, although any bone can be affected."[80] In 1994, the World Health Organization (WHO) defined diagnostic criteria for osteoporosis on the basis of measurement of bone mineral density (BMD) and a comparison to the mean BMD value in young healthy adults of the same gender.[81] Osteoporosis is defined as a BMD value less than 2.5 standard deviations (SD) below the mean BMD in young healthy adults of the same gender (T-score < -2.5). Similarly, osteopenia is defined as a BMD value between 2.5 and 1 SD below the same reference BMD (-2.5 < T-score < -1). Normal BMD is

80 National Osteoporosis Foundation (2004). America's bone health: the state of osteoporosis and low bone mass. 2002. National Osteoporosis Foundation. Washington, DC. 22 Pages.
81 Kanis, J. A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporosis International* 4(6): 368-381.

defined as a BMD value greater than 1 SD below the reference BMD (T-score >-1). Most guidelines and consensus reports suggest using the same criteria for BMD measurements to define the abnormality due to the use of glucocorticoid steroids.

2.1 MECHANISM OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

The problem of glucocorticoid-associated bone loss was first noted over 70 years ago,[82] yet the pathogenic mechanisms are not fully understood. It is known that human bones periodically undergo a remodeling cycle, which involves coupled processes called bone resorption and bone formation. During a normal bone remodeling cycle, the bone mass is resorbed in the first few weeks, which is called bone resorption. Then, new bone mass is restored which lasts for a few months; this is called bone formation. Glucocorticoid steroids moderately increase the process of bone resorption and significantly decrease the process of bone formation.

The evidence of glucocorticoid effects on bone resorption is controversial at the bio-molecular level because the roles and pathways of mediators are not fully established. Some common observations associated with glucocorticoid steroid use include inhibited pituitary gonadotropin production (e.g., decreased levels of estrogen and testosterone), stimulated osteoclastogenesis, an increased life-span of osteoclasts (cells responsible for bone resorption), reduced function and number of osteoblasts (bone forming cells), and decreased osteoblastic signals. The effects of glucocorticoid steroids are more significant on bone formation than on bone resorption. Evidence includes reduced numbers of both osteoblasts and osteoclasts, inhibition of osteoblastogenesis, low rates of mineral apposition and suppressed osteoblast matrix synthesis. Clinically, excess

82 Cushing, H. W. (1932). The basophile adenomas of the pituitary body and their clinical manifestations. *Bulletin of the Johns Hopkins Hospital* 50: 137-195.

exposure to glucocorticoid steroids is associated with a decreased absorption of calcium in the gastrointestinal system, an increased excretion of urinary calcium, a decreased level of serum osteocalcin and alkaline phosphonates, and an increased serum level and activity of parathyroid hormone (PTH).[83, 84, 85, 86, 87, 88] Accordingly, some treatments target problems associated with these clinical observations.

It is important to know that pathogenic mechanisms of glucocorticoid-induced osteoporosis in men and women are similar. It should be noted that mechanisms of glucocorticoid-induced osteoporosis actually differ from those mechanisms of postmenopausal osteoporosis, senile osteoporosis and other secondary osteoporosis. Studies or guidelines on populations with other types of osteoporosis do not directly apply to glucocorticoid users.[89, 90] Therefore, this review primarily focuses on the studies for glucocorticoid users and glucocorticoid-induced osteoporosis. However, for reference purposes, information on postmenopausal osteoporosis is provided if no information was found for glucocorticoid-induced osteoporosis. The next section reviews some important GIOP-related clinical features.

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83 Canalis, E. (1996). Clinical review 83: mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 81(10): 3441-3447.

84 Canalis, E. & Giustina, A. (2001). Glucocorticoid-induced osteoporosis: summary of a workshop. *Journal of Clinical Endocrinology and Metabolism* 86(12): 5681-5685.

85 Canalis, E. & Delany, A. M. (2002). Mechanisms of glucocorticoid action in bone. *Annals of the New York Academy of Sciences* 966: 73-81.

86 Canalis, E. (2003). Mechanisms of glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 15(4): 454-457.

87 Jilka, R. L. (2003). Biology of the basic multicellular unit and the pathophysiology of osteoporosis. *Medical and Pediatric Oncology* 41: 182-185.

88 Patschan, D. *et al*. (2001). Molecular mechanisms of glucocorticoid-induced osteoporosis. *Bone* 29(6): 498-505.

89 Canalis, E. *et al*. (2004). Perspectives on glucocorticoid-induced osteoporosis. *Bone* 34(4): 593-598. .

90 Clowes, J. A. *et al*. (2001). Glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 13(4): 326-332.

2.2 CLINICAL FEATURES OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Risk factors for bone loss include daily and accumulated dose of oral glucocorticoid steroids, prior osteoporotic fractures, older age, vitamin D deficiency, malnutrition, minimal physical (especially weight-bearing) activity and underlying diseases. Compared with the risk factors for other types of osteoporosis, glucocorticoid doses and the underlying diseases are two important factors in glucocorticoid-induced osteoporosis. Therefore, they are reviewed as follows.

2.2.1 Glucocorticoid Doses, Forms and Affected Sites

Significant bone loss may be found as early as one month after the initiation of glucocorticoid therapy even at a relatively low daily dose (i.e., less than 5 mg per day) of prednisone or equivalents.[91, 92, 93] The quick bone loss is probably due to the quickly increased bone resorption. A dose-dependent relationship was found between glucocorticoid doses and bone loss; however, intermittent use of oral glucocorticoid steroids does not reduce the risk of bone loss.[94] The cumulative dose is more important to bone loss than the average dose or duration of therapy.[95] Some researchers argue that no dose of oral glucocorticoid steroids is safe, and recommend that interventions which prevent glucocorticoid-induced bone loss should be used for all glucocorticoid users at

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91 Buckley, L. M. (2000). Clinical and diagnostic features of glucocorticoid-induced osteoporosis. *Clinical and Experimental Dermatology* 18(suppl. 21): S41-S43.

92 Natsui, K. *et al*. (2006). High-dose glucocorticoid treatment induces rapid loss of trabecular bone mineral density and lean body mass. *Osteoporosis International* 17(1): 105-108.

93 van Staa, T. P. *et al*. (2001). Public health impact of adverse bone effects of oral corticosteroids. *British Journal of Clinical Pharmacology* 51(6): 601-607.

94 Canalis, E. (2003). Mechanisms of glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 15(4): 454-457.

95 van Staa, T. P. *et al*. (2000). Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology* 39(12): 1383-1389.

any dose.[96, 97, 98] Therefore, this study targets glucocorticoid user who receive at least three months of glucocorticoid therapy, with a additional consideration for high-risk users who receive a higher cumulative glucocorticoid dose.

Different forms of glucocorticoid steroids have different impacts on bone loss. The oral form is the frequently used form which has a systemic effect. Research compared the risk of osteoporotic fractures among different glucocorticoid forms, and showed that the use of oral glucocorticoid steroid has higher increased risks than other forms.[99] The topical or inhaled forms of glucocorticoid steroids seem to have less effect on bone loss than the oral form.[100, 101, 102]

Glucocorticoid steroids affect bones at the spine, hip and wrist, but the risk of vertebral fractures is higher than that of non-vertebral fractures in glucocorticoid users. For example, a study indicated that about 72% of all vertebral fractures and 47% of all hip fractures were associated with use of glucocorticoid steroid.[103] Glucocorticoid-induced bone loss occurs faster in trabecular bone (primarily in the spine and ribs) than in cortical bone (e.g., hip and long bones). The rate of bone loss in trabecular bone in glucocorticoid users is about 10-20% in the first three to six months of glucocorticoid therapy and about two percent per year thereafter; bone loss at the femoral

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96 Adachi, J. D. & Ioannidis, G. (2000). Glucocorticoid-induced osteoporosis. *Drug Development Research* 49: 120-134.

97 Buckley, L. M. (2000). Clinical and diagnostic features of glucocorticoid-induced osteoporosis. *Clinical and Experimental Dermatology* 18(suppl. 21): S41-S43.

98 Clowes, J. A. *et al.* (2001). Glucocorticoid-induced osteoporosis. *Current Opinion in Rheumatology* 13(4): 326-332.

99 Steinbuch, M. *et al.* (2004). Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporosis International*, 15(4): 323-328.

100 *Ibid.*

101 van Staa, T. P. *et al.* (2001). Use of inhaled corticosteroids and risk of fractures. *Journal of Bone and Mineral Research* 16(3): 581-588.

102 Allen, D. B. (2002). Safety of inhaled corticosteroids in children. *Pediatric Pulmonology* 33: 208-220.

103 van Staa, T. P. *et al*. (2001). Public health impact of adverse bone effects of oral corticosteroids. *British Journal of Clinical Pharmacology* 51(6): 601-607.

neck remains constant over time (2-3% per year).[104] When glucocorticoid therapy is discontinued, the bone loss caused by using glucocorticoid steroids is unlikely to be completely recovered, but the rate of bone loss and the risk of osteoporotic fractures could be decreased.[105]

2.2.2 Underlying Diseases in Glucocorticoid Users

The underlying diseases, for which glucocorticoid steroids were prescribed, have a confounding effect on bone loss. Both glucocorticoid use and the underlying condition(s) contribute to the bone loss, so the net effect of glucocorticoid use on bones is not easily singled out.[106] Therefore, direct comparisons among studies of glucocorticoid use with different diseases should be made with caution. Two reviews summarized various risks of developing glucocorticoid-induced osteoporosis, vertebral fractures and hip fractures in glucocorticoid users with different underlying diseases.[107, 108] Musculoskeletal (e.g., 67.1% of subjects of all studies in van Staa's review) and pulmonary diseases (15.7%) account for the major categories of underlying conditions in the samples of many studies. They are followed by organ transplantations, gastrointestinal, renal and hepatic diseases.

Glucocorticoid dosing and use patterns and the comorbidities of glucocorticoid users are factors to be considered in studies for glucocorticoid-induced osteoporosis.

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104 Buckley, L. M. (2000). Clinical and diagnostic features of glucocorticoid-induced osteoporosis. *Clinical and Experimental Dermatology* 18(suppl. 21): S41-S43.

105 *Ibid.*

106 van Staa, T. P. *et al*. (2001). Public health impact of adverse bone effects of oral corticosteroids. *British Journal of Clinical Pharmacology* 51(6): 601-607.

107 Boling, E. P. (2004). Secondary osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clinical Therapeutics* 26(1): 1-14.

108 van Staa, T. P. *et al*. (2002). The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporosis International* 13(10): 777-787.

The next question is: Why should we care about glucocorticoid-induced osteoporosis? The following section highlights the magnitude of this condition.

2.3 MAGNITUDE OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS AND FRACTURES

Epidemiological data show the importance of the effects of glucocorticoid steroid use. An important consequence of glucocorticoid-induced osteoporosis is the development of fractures, which result in increased risks of immobility or death. In this section, a review of GIOP-related epidemiology, including incidence, fracture risks, disability and mortality, is provided.

2.3.1 Prevalence

There is no current estimate of the number of long-term glucocorticoid users in the United States. However, recent estimates indicate that about 0.7% of the general population in Iceland took glucocorticoid steroids for at least three months, and that 0.9% of the general population in the U.K. had received oral glucocorticoid therapy.[109, 110] If these percentages are projected to the population in the United States, the number of Americans receiving long-term glucocorticoid therapy could be 2.04 to 2.62 million, based on the total U.S. population of 290.85 million in 2003.

Although the size of the vulnerable population seems relatively small, the magnitude of threats caused by glucocorticoid steroids is relatively large. The most common threat after the development of bone loss is osteoporotic fracture. In the

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109 Gudbjornsson, B. *et al*. (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

110 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

cross-sectional study in Iceland, 20% of long-term steroid users had osteoporosis or osteopenia (low bone mass), and 26% had fragility fractures.[111] In France, the incidence rates of all osteoporotic fractures during 2001 were 7,567 (95% CI 7,519-7,615) and 2,312 (95% CI 2,283-2,341) per one million women and men aged over 45 years, respectively.[112] Based on these estimates, there would be approximately 0.41 to 0.52 million Americans with GIOP and 0.53 to 0.68 million with osteoporotic fractures. Next, the relative risks of osteoporotic fracture are reviewed.

2.3.2 Fracture Risks

Oral glucocorticoid use increases risks of osteoporotic fractures. Many studies have estimated the relative risks (RRs) of various osteoporotic fractures in glucocorticoid users. Steinbuch *et al.* evaluated fracture risks in patients exposed to oral glucocorticoid steroids by using an administrative claims database.[113] The adjusted relative risks (RR) are 1.87 (95% CI 1.2-2.9) for hip fractures, 2.92 (95% CI 2.0-4.3) for vertebral fractures, 1.03 (95% CI 0.8-1.4) for wrist/forearm fractures, 1.68 (95% CI 1.5-1.9) for non-vertebral fractures or 1.75 (95% CI 1.6-1.9) for any fractures. The same study also reported the relative risks of any fracture by gender and age groups. Overall, the relative risks of any fracture are 1.50 for men (95% CI 1.28-1.75) and 2.21 for women (95% CI 1.94-2.51). The relative risks increase with increased age overall: 1.59 (95% CI 1.18-2.14) for subjects aged 18-30 years old, 1.86 (95% CI 1.51-2.28) for subjects

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111 Gudbjornsson, B. *et al*. (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

112 Maravic, M. *et al*. (2005). Incidence and cost of osteoporotic fractures in France during 2001. a methodological approach by the national hospital database. *Osteoporosis International* 16(12): 1475-1480.

113 Steinbuch, M. *et al*. (2004). Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporosis International*, 15(4): 323-328.

aged 31-44 years old, 1.89 (95% CI 1.58-2.27) for subjects aged 45-54 years old and 2.02 (95% CI 1.71-2.40) for subjects aged 55-64 years old.

The increased relative risks are dependent on glucocorticoid doses. A case-control study (cases=124,655 controls=373,962) was conducted in Denmark to investigate relative risks associated with use of glucocorticoid steroids in any formulation and administration.[114] With respect to oral glucocorticoid steroids, compared to background-matched non-glucocorticoid users, the overall adjusted odds ratios (OR) were 0.97 (95% CI 0.93-1.01) for subjects using less than 2.5 mg of prednisone (or its equivalents) per day, 1.15 (95% CI 1.09-1.22) for subjects using prednisone between 2.5 mg and 7.49 mg per day, and 1.59 (95% CI 1.49-1.70) for subjects using more than 7.5 mg of prednisone per day. Among fractures at different sites, vertebral fractures have the highest increased OR (2.08, 95% CI 1.54-2.79 in subjects using more than 7.5 mg of prednisone, for example), followed by hip fractures (1.45 95% CI 1.25-1.69 in the 7.5 mg group) and wrist fractures (1.19 95% CI 0.99-1.43 in the 7.5 mg group).

The study with the largest sample size included 244,235 oral glucocorticoid users and 244,235 controls from the U.K. General Practice Research Database (GPRD).[115] The relative risk of all fractures was 1.33 (95% confidence interval [CI] 1.29-1.38); specifically, the relative risks of vertebral, hip or wrist fractures were 2.60 (95% CI 2.31-2.92), 1.61 (95% CI 1.47-1.76) and 1.09 (95% CI 1.01-1.17), respectively. A meta-analysis was conducted to provide the pooled relative risks of osteoporotic fractures in a total of 66 studies involving 2,891 glucocorticoid users.[116] The pooled RRs were

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114 Vestergaard, P. *et al*. (2003). Corticosteroid use and risk of hip fracture: a population-based case-control study in Denmark. *Journal of Internal Medcine* 254: 486-493.

115 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids and risk of fractures. *Journal of Bone and Mineral Research* 15(6): 993-1000.

116 van Staa, T. P. *et al*. (2002). The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporosis International* 13(10): 777-787.

1.91 (95% CI 1.68-2.15) for all fractures, 2.86 (95% CI 2.56-3.16) at the spine, 2.01 (95% CI 1.74-2.29) at hip and 1.13 (95% CI 0.66-1.59) at wrist. The pooled RRs are larger than those in the U.K. study; this may have resulted from a smaller sample size in the meta-analyses, different sample characteristics, or different criteria for recruiting samples. Compared to non-glucocorticoid users, glucocorticoid users have a two-to three-times higher risk of vertebral fractures, about two-times higher risk of hip fractures and an increased risk of other fractures.

Kanis, Johnell and colleagues also reported 10-year probabilities of osteoporotic fractures in the Swedish population by age and BMD t-scores.[117] The risks of fractures are different by gender, age, affected sites and BMD t-scores. The probabilities of fractures in women are higher than those in men. The average 10-year probabilities of any osteoporotic fracture ranging from 2.6% to 13.1% in men with increasing age from 45 years old to 85 years old, and ranging from 3.8% to 27.0% in women with increasing age from 45 years old to 85 years old. As expected, those with lower BMD t-scores have higher probabilities than those with higher BMD t-scores at the same gender and age. Compared to subjects with normal BMD (t-score =0), subjects with BMD t-scores below 2.5 have approximately a three-fold increased risk of any fractures.

Vertebral fractures are often under-diagnosed, unless significant clinical symptoms (e.g., back pain) are observed.[118] As mentioned in Section 2.2.1, glucocorticoid use induces more bone loss at trabecular bone than other sites within the first year of glucocorticoid therapy. The actual risk of vertebral fractures in

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117 Kanis, J. A. *et al*. (2001). Ten Year Probabilities of Osteoporotic Fractures According to BMD and Diagnostic Thresholds. *Osteoporosis International*, 989-995.

118 Melton, L. J. III *et al*. (1993). Prevalence and incidence of vertebral deformities. *Osteoporosis International* 3(3): 113-119.

glucocorticoid users could be higher than reported values in the literature. Similarly, it has been argued that the lifetime risks of hip fractures are also under-estimated.[119]

2.3.3 Disability and Mortality

Osteoporosis was found to be associated with disability.[120] The estimated global prevalence of hip fractures with disability was 4.48 million in 1990.[121] Evidence shows that mortality rates after fractures were significantly higher in patients with osteoporosis than in the general population.

A few studies were found to specifically address mortality in glucocorticoid users. However, various underlying diseases may have a confounding attribution to deaths caused by osteoporotic fractures, so it is difficult to compare mortality rates among glucocorticoid steroid users with different disease conditions. Nevertheless, the trends of post-fracture mortality in other types of osteoporosis may, to some extent, help with projection of mortality due to glucocorticoid-induced osteoporosis.

Glucocorticoid users have an increased risk of mortality compared to non-glucocorticoid users, and the increases are dose-dependent. Schols *et al.* compared mortality rates among severe chronic pulmonary disease (COPD) patients who used oral glucocorticoid steroids to the rates of those who did not.[122] Compared to non-glucocorticoid users, the relative risks (RR) of mortality are: 2.279 (95% CI

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119 Oden, A. *et al*. (1998). Lifetime risk of hip fracture is underestimated. *Osteoporosis International* 8(6): 599-603.

120 Wagemans, A. M. A. *et al*. (1998). Osteoporosis and intellectual disability: is there any relation? *Journal of Intellectual Disability Research* 42(5): 370-374.

121 Johnell, O. & Kanis, J. A. (2004). An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporosis International* 15(11): 897-902.

122 Schols, A. M. W. J. *et al*. (2001). Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *European Respiratory Journal* 17(3): 337-342.

0.902-5.762) for 5 mg oral steroid users, 2.340 (95% CI 1.235-4.435) for 10 mg oral steroid users and 4.031 (95% CI 1.994-8.149) for 15 mg oral steroid users. Sihvonen *et al.* evaluated mortality in patients with rheumatoid arthritis who used low dose oral glucocorticoid steroids.[123] Compared to non-glucocorticoid users, the RR of mortality in oral glucocorticoid users are 1.14 (95% CI 0.98-1.27, p=0.057) for one-year treatment, and 1.69 (95% CI 1.12-2.56, p=0.011) for treatment over 10 years.

The mortality rates after osteoporotic fractures vary by affected sites. The mortality of vertebral fractures is usually the highest, followed by hip and then wrist fractures. For example, Johnell, Kanis and colleagues reported that the one-year survival rates after osteoporotic fractures in Sweden were 72% for vertebral fractures, 78% for hip fractures and 94% for wrist fractures.[124] Jonell's study also indicated that mortality rates increase with increased age and number of years after fractures. Another study showed that the relative risks of age-adjusted mortality following fractures were 8.64 (95% CI 4.45-16.74) for vertebral fractures, 6.68 (95% CI 3.08-14.52) for hip fractures and 2.15 (95% CI 1.36-3.42) for all fractures.[125]

The role of gender in mortality rates is unclear. Both unadjusted and age-adjusted excess post-fracture mortality rates in men are usually higher than those in

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123 Sihvohen, S. *et al*. (2006). Mortality in patients with rheumatoid arthritis treated with low-dose oral glucocorticoids. a population-based cohort study. *Journal of Rheumatology* 33(9): 1740-1746.

124 Johnell, O. *et al*. (2004). Mortality after osteoporotic fractures. *Osteoporosis International* 15(1): 38-42.

125 Cauley, J. A. *et al*. (2000). Risk of mortality following clinical fractures. *Osteoporosis International* 11(7): 556-561.

women in two studies.[126, 127] However, after adjustment for gender-specific population risks, Johnell *et al.* found no difference in mortality between males and females.[128]

No study was found for investigation of differences in mortality rates between anti-osteoporotic treatments and non-treatment in glucocorticoid users. However, Cree *et al.* conducted a study which investigated mortality and morbidity associated with osteoporotic treatments after hip fractures in the general population of Alberta.[129] The study used administrative claims data, data for emergency room visits and the morbidity database in Alberta, and divided subjects into one of six treatment groups: hormones, bisphosphonates (including Didronel® and Fosamax®, but excluding Actonel®), calcitonin, vitamin D_3, raloxifene and no treatment. Similar incidence rates of hip fracture and rates of hospitalization were found between treated and untreated patients. Overall, subjects in the treatment groups had a significant lower mortality rate than untreated patients (OR=0.34 95% CI 0.17-0.70).

Given the epidemiological data related to glucocorticoid-induced osteoporosis, the consequences of using glucocorticoid steroids are potentially severe. Therefore, glucocorticoid users should receive proper intervention to manage bone loss and associated consequences. In the next section, results from randomized clinical trials (RCTs) of each medication used for glucocorticoid-induced osteoporosis are reviewed.

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126 Center, J. R. *et al*. (1999). Mortality after all major types of osteoporotic fracture in men and women: an observational study. *The Lancet* 353(9156): 878-882.

127 Forsen, L. *et al*. (1999). Survival after hip fracture: short-and long-term excess mortality according to age and gender. *Osteoporosis International* 10(1): 73-78.

128 Johnell, O. *et al*. (2004). Mortality after osteoporotic fractures. *Osteoporosis International* 15(1): 38-42.

129 Cree, M. W. *et al*. (2003). Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteoporosis International* 14(9): 722-727.

2.4 CLINICAL EVALUATION OF PHARMACOTHERAPY

Pharmaceutical agents frequently used for osteoporosis are often classified into seven groups: (1) calcium, vitamin D and their combinations; (2) bisphosphonates (BP); (3) hormone replacement therapy (HRT); (4) selective estrogen receptor modulators (SERMs); (5) calcitonin; (6) anabolic agents; and (7) combination therapy. For each medication, the clinical outcomes in randomized clinical trials (RCTs) are highlighted. Clinical outcomes are limited to differences in bone mineral density (BMD) and fracture risks between study arms in glucocorticoid users in this review.

2.4.1 Calcium, Vitamin D and Their Combinations

Daily calcium plus vitamin D supplements are frequently recommended by many studies, guidelines or textbooks for people who are vulnerable to bone loss and osteoporotic fractures. The calcium element in supplements is commonly provided in the carbonate or citrate form; some brand name products include Tums®, Caltrate®, Citracal® and Solgar®. Vitamin D helps the body absorb calcium from the intestines and prevents its excessive excretion in the urine. Vitamin D contains a range of compounds, including vitamin D_1 (calciferol), vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), vitamin D_4, vitamin D_5, vitamin D_c, and vitamin D_m. The term "plain" or "inactivated" vitamin D usually refers to vitamin D_2 (ergocalciferol), which is derived from plants or yeasts, or vitamin D_3 (cholecalciferol), which is derived from animal sources. The "plain" vitamin D has to be activated to 1, 25-dihydroxy vitamin D (activated forms) by enzymes in the liver and kidneys. Alfacalcidol (1-alpha-hydroxycholecalciferol), calcitriol (Rocaltrol®) and calcifediol (Calderol®) are examples of analogues of active vitamin D_3 metabolites.

- Calcium, Vitamin D and their Combinations for osteoporosis

A review indicated that using calcium decreases further bone loss, but does not reduce fracture risks, and also indicated that vitamin D reduces fracture risks slightly but does not affect BMD.[130] It suggests that the combination of calcium and vitamin D may have a protective effect regarding both BMD and fractures in the elderly. However, in a recent trial recruiting 811 men and 4,481 women aged more than 70 years old who were followed for 24 to 62 months, there were no significant differences in hazard ratios among groups receiving 800 IU of vitamin D_3 alone, 1,000 mg of calcium alone, the combination of calcium/vitamin D, or placebo.[131] In another RCT recruiting 3,314 women aged 70 years or over with at least one risk factor for hip fractures, subjects were provided a combination of 800 IU of vitamin D_3 (cholecalciferol)/1,000 mg of calcium with an information leaflet (the study group) or an information leaflet alone (the control group).[132] No significant differences in risk of all fractures and quality of life measures were found between groups. Because of the non-significant results and some adverse outcomes observed, this study did not support the use of daily calcium and plain vitamin D_3 (alone or in combination) in independent elderly people. These studies targeted osteoporosis in general and the results are not necessarily applicable to glucocorticoid-induced osteoporosis.

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130 Meunier, P. J. (1999). Calcium, vitamin D and vitamin K in the prevention of fractures due to osteoporosis. *Osteoporosis International* 9(suppl. 1): S48-S52.

131 The RECORD Trial Group. (2005). Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *The Lancet* 365(9471): 1621-1628.

132 Porthouse, J. *et al*. (2005). Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *British Medical Journal* 330(7498): 1003-1008.

- Calcium, Vitamin D and their Combinations for glucocorticoid-induced osteoporosis

Alfacalcidol and calcitriol, which are vitamin D_3 analogues, have received much attention recently in studies involving glucocorticoid users. Ringe *et al.* reviewed some early RCTs for alfacalcidol and calcitriol, and suggested that activated vitamin D_3 should be recommended for the prevention and treatment of glucocorticoid-induced osteoporosis.[133] Ringe *et al.* also conducted a three-year prospective matched study recruiting long-term glucocorticoid users who received 500 mg of calcium, and they found that the group who received one microgram (mcg) of alfacalcidol showed a small but significant increase in spine BMD and a significant reduction of back pain in comparison with the control group who received 1,000 IU of plain vitamin D.[134] Similarly, a subsequent expanded study by Ringe *et al.* suggested that the groups receiving one mcg of alfacalcidol and 500 mg of calcium had significant increases in BMD values at the spine and femoral neck, had significant reductions of vertebral (RR =0.61, 95% CI 0.24-0.81) and non-vertebral fractures (RR =0.41, 95% CI 0.06-0.68), and showed a significant reduction in back pain when compared to the control group who received 1,000 IU of plain vitamin D with 500 mg of calcium.[135] Ringe *et al.* concluded that alfacalcidol is "superior" for glucocorticoid-induced osteoporosis to other vitamin D derivatives. However, Barthel *et al.* argued that the comparisons in Ringe's studies were unfair because they compared a maximal dose of alfacalcidol with the dose

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133 Ringe, J. D. (1997). Active vitamin D metabolites in glucocorticoid-induced osteoporosis. *Calcified Tissue International* 60(1):124-127.

134 Ringe, J. D. *et al*. (1999). Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. *Calcified Tissue International* 65(4): 337-340.

135 Ringe, J. D. *et al*. (2004). Superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis. *Rheumatology International* 24(2): 63-70.

of vitamin D that is too small to show a significant effect on glucocorticoid-induced osteoporosis.[136]

In a 28-day RCT for calcitriol, 48 normally healthy male volunteers aged 21 to 54 years randomly received calcitriol alone, prednisolone alone, a combination or placebo in turns.[137] The results suggested a partial prevention effect of calcitriol on glucocorticoid-induced osteoporosis. However, in a recent two-year RCT recruiting 108 patients with moderate asthma who took inhaled glucocorticoid steroids, no significant difference in BMD values at the lumbar spine and femoral neck was found between the calcitriol (0.25 mg) group and the matched placebo group.[138]

Amin *et al.* conducted a meta-analysis comparing the efficacy of vitamin D, active vitamin D_3 and its analogues with calcium alone or bisphosphonates in RCTs (for at least six months) for the prevention and/or treatment of glucocorticoid-induced osteoporosis, and they concluded that vitamin D plus calcium combination was better than calcium alone or no treatment, but "inferior" to bisphosphonates.[139] Barthel *et al.* argued that four out of six studies in that meta-analysis also included vitamin D in the bisphosphonate group, so the authors' conclusion is "unsupported."[140] Recently, another meta-analysis was conducted to compare the efficacy of vitamin D_3 preparations with other anti-osteoporosis therapies for glucocorticoid-induced osteoporosis by

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136 Barthel, H. R. & Vieth, R. (2004). Lack of generalizable evidence of the superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis: comment on the article by Ringe *et al. Rheumatology International* 24(4): 250-251.

137 Gram, J. *et al*. (1998). Effects of short-term treatment with prednisolone and calcitriol on bone and mineral metabolism in normal men. *Bone* 23(3): 297-302.

138 McDonald, C. F. *et al*. (2006). Calcitriol does not prevent bone loss in patients with asthma receiving corticosteroid therapy: a double-blind placebo-controlled trial. *Osteoporosis international* 17(10): 1546-1551.

139 Amin, S. *et al*. (1999). The role of vitamin D in corticosteroid-induced osteoporosis. *Arthritis and Rheumatism* 42(8): 1740-1751.

140 Barthel, H. R. & Schacht, E. (2000). Vitamin D in corticosteroid-induced osteoporosis. *Arthritis and Rheumatism* 43(5): 1188-1189.

including more RCTs.[141] The pooled relative risk for vertebral fractures of active vitamin D_3 analogues was 0.56 (95% CI 0.34-0.92), compared with placebo, plain vitamin D and/or calcium, or 1.20 (95% CI 0.32-4.55), compared with bisphosphonates. However, the authors inappropriately concluded that the efficacy of vitamin D_3 analogues is less than that of bisphosphonates. The efficacy of active vitamin D_3 and its analogues for glucocorticoid-induced bone loss is inconclusive.

Overall, evidence on calcium, vitamin D (plain or active forms or analogues) and the combination shows no or minimal protective effects on bone loss and fracture risks in glucocorticoid users. It is generally believed that the addition of anti-osteoporotic agents to calcium and vitamin D (or their combination) should result in an additional benefit for the management of osteoporosis. A daily supplementation of 1,500 milligrams (mg) of calcium and 400 International Units (IU) of vitamin D is recommended for glucocorticoid-induced osteoporosis.[142]

However, in many studies, the reported outcomes of an anti-osteoporotic agent actually reflect the synergistic effects of calcium/vitamin D and the anti-osteoporotic agent. Additionally, the dosage regimens of calcium/vitamin D vary across studies. Therefore, the efficacy and/or effectiveness of an anti-osteoporotic agent should be interpreted or compared with special caution. The next few sections review the efficacy of other anti-osteoporotic agents on glucocorticoid-induced osteoporosis.

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141 de Nijs, R. N. J. *et al*. (2004). Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D_3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. *Osteoporosis International* 15(8): 589-602.

142 American College of Rheumatology. (1996). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on osteoporosis guidelines. *Arthritis and Rheumatism* 39(11): 1791-1801.

2.4.2 Bisphosphonates (BP)

- Alendronate

Alendronate has been shown to increase the BMD and reduce risks of osteoporotic fractures in studies of glucocorticoid users with various underlying diseases. In an RCT recruiting 43 men and premenopausal women with sarcoidosis, 15 patients (the glucocorticoid group) were treated by glucocorticoid therapy for six to 12 months, 15 patients (the alendronate/glucocorticoid group) were simultaneously prescribed glucocorticoid and 5 mg of alendronate daily and 13 patients received no treatment (controls). The alendronate/glucocorticoid group had significant increases in BMD in comparison with the glucocorticoid group (+0.8%) and the control group (+4.5%).[143] In a six-month RCT recruiting 25 heart transplant recipients, those who received 10 mg of alendronate per day (starting two months after transplantation) had a significant increase in BMD (at total body, hip and spine) compared to those who had no alendronate therapy.[144] Similarly, in a two-year RCT recruiting 58 renal transplant recipients, 29 patients (with relatively low BMD values) had a significant increase in BMD compared to their previous values after one year of alendronate treatment at a dose of 10 mg per day; yet a significant increase was not found in the control group.[145]

In a 48-week multi-center, multi-country RCT recruiting 477 patients with long-term glucocorticoid use and taking 800-1,000 mg of calcium and 250-500 IU of vitamin D per day, those who used alendronate (5-10 mg daily) had significant increases

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143 Gonnelli, S. *et al*. (1997). Prevention of corticosteroid-induced osteoporosis with alendronate in sarcoid patients. *Calcified Tissue International* 61(5): 382-385.

144 Braith, R. W. *et al*. (2003). Resistance exercise training and alendronate reverse glucocorticoid-induced osteoporosis in heart transplant recipients. *The Journal of Heart and Lung Transplantation* 22(10): 1082-1090.

145 Cruz, D. N. *et al*. (2002). Treatment of osteoporosis and osteopenia in long-term renal transplant patients with alendronate. *American Journal of Transplantation* 2(1): 62-67.

in BMD at the spine, hip and wrist in comparison with the placebo controls.[146] The incidence rates of fractures after one-year alendronate treatments were 3.0% (2.7% in men and 4.4% in women) in treatment groups and 5.9% (2.1% in men and 13% in women) in the placebo group. It is likely that alendronate increases BMD but fails to reduce the incidence rates of vertebral fractures in glucocorticoid users.

The same research group conducted a one-year extended RCT by using the same design, and recruited 66 male and 142 female glucocorticoid users who were enrolled in the previous study.[147] Study subjects who received alendronate still showed significantly increased BMD at the spine when compared with the control groups. Evidence indicates the reduction in BMD occurred as early as three months after initiation of alendronate therapy. A reduction of vertebral fractures was also observed in comparison of alendronate group to the controls. After one-year alendronate treatments, the incidence rates of vertebral fractures were 0.7% in the treatment group and 6.8% in the control group (p=0.026). After two years of alendronate treatment, no vertebral fracture was found in the treatment group.[148]

Lems *et al.* conducted an RCT to investigate the efficacy of alendronate in patients with rheumatoid arthritis who used low-dose prednisone.[149] No significant difference in prevalence rates of vertebral fractures was found between the two comparison groups (54% in alendronate group and 39% in the placebo group) after

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146 Saag, K. G. *et al*. (1998). Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *New England Journal of Medicine* 339(5): 292-299.

147 Adachi, J. D. *et al*. (2001). Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis and Rheumatism* 44(1): 202-211.

148 *Ibid.*

149 Lems, W. F. *et al.* (2006). Positive effect of alendronate on bone minieal density and makers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. *Osteoporosis International* 17: 716-723.

one-year follow-up. There was also no significant difference in incidence rates of vertebral fractures between the two comparison groups (13% in alendronate group and 4% in the placebo group). Although the differences are not significant, it is noted that both rates for alendronate group are higher than those for the placebo group.

In a three-year RCT recruiting 2,027 postmenopausal women with prior vertebral fractures, those who received 5 mg of alendronate daily for two years and then 10 mg of alendronate daily for one additional year had significantly lower risks of new fractures (any fracture RR =0.72, 95% CI 0.58-0.90; vertebral RR =0.53, 95% CI 0.41-0.68; hip RR =0.49, 95% CI =0.23-0.99; wrist RR =0.52, 95% CI 0.31-0.87) than those in the placebo control group.[150] An important RCT for postmenopausal osteoporosis is the Fracture Intervention Trial (FIT),[151, 152, 153, 154, 155] and the conclusions were similar to those in studies for glucocorticoid-induced osteoporosis.

- Risedronate

Risedronate also shows protective effects similar to those of alendronate. In a one-year multi-center, double-blind RCT recruiting 224 men and women who received 500 mg of calcium daily and long-term glucocorticoid therapy, risedronate groups

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150 Black, D. M. *et al*. (1996). Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *The Lancet* 348(9041): 1535-1541.

151 *Ibid.*

152 Cummings, S. R. *et al*. (1998). Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *Journal of the American Medical Association* 280(24): 2077-2082.

153 Hochberg, M. C. *et al.* (1999). Larger increases in bone mineral density during alendronate therapy are associated with a low risk of new vertebral fractures in women with postmenopausal osteoporosis. *Arthritis and Rheumatism* 42(6): 1246-1254.

154 Chrischilles, E. A. *et al*. (2001). The effect of alendronate on fracture-related healthcare utilization and costs: the Fracture Intervention Trial. *Oestoporos International* 12(8): 654-660.

155 Levis, S. *et al*. (2002). Alendronate reduces the risk of multiple symptomatic fractures: results from the Fracture Intervention Trial. *Journal of the American Geriatrics Society* 50(3): 409-415.

showed a significantly higher BMD (both 2.5-mg and 5-mg groups) and a significantly lower incidence of vertebral fractures (5-mg group only) in comparison with controls.[156] The incidence rates of vertebral fractures after one-year risedronate treatments were 5.7% in the treatment group and 17.3% in the placebo group. Another one-year RCT in 23 sites in Europe recruited men and women aged 18 to 85 years old who received glucocorticoid therapy at a minimum daily dose of 7.5 mg of prednisone for more than six months.[157] Significant differences in BMD were found at lumbar spine ($p<0.001$), femoral neck ($p=0.004$) and trochanter ($p=0.010$) between risedronate and the placebo groups). The incidence rates of vertebral fractures were 5% in each of two groups receiving 2.5-mg and 5-mg of risedronate, respectively, for one year, and 15% in the placebo group; however, the differences are not significant ($p=0.125$). If these two risedronate groups are combined, the reduction of vertebral fractures (70%) in the combined risedronate group is significant ($p=0.042$).

Because the sample size in each of the risedronate groups was relatively small, it may result in insufficient statistical power to detect differences in incidence rates of vertebral fractures between comparison groups. In studies investigating the efficacy of risedronate for postmenopausal osteoporosis, similar patterns emerged.[158] The findings of studies for postmenopausal osteoporosis may still serve as a reference. The notable

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156 Cohen, T. *et al*. (1999). Risedronate therapy prevents corticosteroid-induced bone loss. *Arthritis and Rheumatism* 42(11): 2309-2318.

157 Reid, D. M. *et al.* (2000). Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. *Journal of Bone and Mineral Research* 15(6): 1006-1013.

158 Reginster, J.-Y. *et al*. (2000). Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporosis International* 11(1): 83-91.

RCT that evaluated efficacy of risedronate for postmenopausal osteoporosis is the Vertebral Efficacy with Risedronate Therapy (VERT) Study.[159, 160]

- Other bisphosphonates

Three RCTs evaluating other bisphosphonates for glucocorticoid-induced osteoporosis were found. Adachi *et al.* conducted a one-year RCT of intermittent etidronate in 141 men and women aged 19 to 87 years old who recently received high-dose glucocorticoid therapy. Each subject in the etidronate group received four cycles of intermittent treatments; in each cycle, subjects were provided 400 mg of etidronate per day for 14 days and then 500 mg of calcium per day for 76 days. Significant differences in BMD were found between etidronate and the placebo groups at lumbar spine (p=0.02) and at trochanter (p=0.02), but not at femoral neck (not significant). Among post-menopausal female subjects, a reduction (85%) in incidence rates of vertebral fractures was found between etidronate and placebo groups (p=0.05).

In another one-year RCT recruiting glucocorticoid users who received 800 mg of calcium daily, 14 patients receiving intermittent intravenous pamidronate (30 mg every three months) had a significant increase in BMD compared to the 13 control subjects.[161] In a four-year double-blind RCT recruiting patients with arthritis and osteoporosis who received 1,000 mg of calcium and 800 IU of vitamin D supplements daily, 84 patients who received 100 mg of intramuscular clodronate once per week had a significant

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159 Harris, S. T. *et al*. (1999). Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial, the Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *Journal of the American Medical Association* 282(14): 1344-1352.

160 Reginster, J.-Y. *et al*. (2000). Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporosis International* 11(1): 83-91.

161 Boutsen, Y. *et al*. (1997). Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. *Calcified Tissue International* 61(4): 266-271.

reduction of vertebral fractures (RR =0.63, 95% CI 0.35-0.98 for vertebral; RR =0.25, 95% CI 0.15-0.91 for multiple vertebral) compared to the 79 control subjects.[162]

Currently, alendronate and risedronate are the only prescription medications approved by the FDA for the prevention and treatment of glucocorticoid-induced osteoporosis. Alendronate (Fosamax® by Merck) is available in tablets (5, 10, 35, 40 and 70 mg), solution (75 ml equivalent to 70 mg) and a tablet combined with cholecalciferol (Fosamax plus D®). Risedronate (Actonel® by Procter and Gamble) is available in a tablet form (5, 30 and 35 mg). Etidronate (Didronel® by Procter and Gamble) was approved by the FDA for treating Paget's disease (but not for osteoporosis); it is available for the treatment of bone pain due to osteoporosis in Canada and Europe. Table 2.1 shows the dosing regimens, indications and approval dates for FDA-approved bisphosphonates.

In conclusion, the protective effects of alendronate and risedronate for glucocorticoid-induced osteoporosis have been supported. The efficacy of other bisphosphonates for glucocorticoid-induced osteoporosis is still under evaluation, but positive results are expected. Although bisphosphonates have shown significant protective effects on bone loss and fracture risks, estrogens or hormone replacement therapy (HRT) had been used widely for preventing osteoporosis, especially in postmenopausal women. The next section reviews the efficacy of HRT for osteoporosis.

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162 Frediani, B. *et al*. (2003). Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone* 33(4): 575-581.

2.4.3 Hormone Replacement Therapy (HRT)

Hormone replacement therapy (HRT) was frequently used to manage osteoporosis. Only a few small prospective studies were found that evaluated the efficacy of HRT in glucocorticoid users. The efficacy of HRT was evaluated in postmenopausal women with rheumatoid arthritis who used or did not use low-dose glucocorticoid steroids.[163] One hundred subjects received HRT (the HRT groups) and another 100 subjects received daily 400 mg calcium supplementation (the calcium group). Twenty-one subjects in each group received glucocorticoid steroids (GS). Overall, a significant difference in BMD were found at lumber spine between the HRT and calcium groups after two-year treatments (HRT: +2.22%, 95% CI +0.72% to +3.72%; calcium -1.19%, 95% CI -2.29% to -0.09%, $p<0.001$). Subjects in the GS-HRT group had a significant increase in BMD at lumber spine (+3.75%, 95% CI +0.72% to +6.78%) after two-year treatments; however, no significant difference in BMD was found between GS-HRT and GS-calcium groups.

163 Hall, G. M. *et al.* (1994) Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis and Rheumatism* 37(10): 1499-1505.

Table 2.1 Dosing regimens, indications and approval dates for approved bisphosphonates

Brand name (generic name) and manufacturer **Dosing regimen**	**Indication**[§]	**Approval date**†
Fosamax® (alendronate sodium) by Merck		
5 mg oral tablet/day	PMO-prevention	09/29/1995
	GIOP -treatment	06/16/1999
10 mg oral tablet/day	PMO-treatment	06/08/1999
	OP/men-treatment	09/29/2000
	GIOP-treatment (women no HRT)	06/16/1999
35 mg oral tablet/week	PMO-prevention	10/20/2000
40 mg oral tablet/day for 6 months	Paget's disease	06/08/1999
70 mg oral tablet/week	PMO-treatment	10/20/2000
	OP/men-treatment	01/31/2001
70 mg/75 ml oral solution/week	PMO-treatment	09/17/2003
	OP/men-treatment	09/17/2003
Fosamax plus D® (alendronate sodium and cholecalciferol) by Merck		
70 mg/2,800 IU oral tablet/week	PMO-treatment	04/07/2005
	OP/men-treatment	04/07/2005
Actonel® (risedronate sodium) by Procter and Gamble		
5 mg oral tablet/day	PMO-prevention	04/14/2000
	PMO-treatment	04/14/2000
	GIOP-prevention	04/14/2000
	GIOP-treatment	04/14/2000
30 mg oral tablet/day for 2 months	Paget's disease	03/07/1998
35 mg oral tablet/week	PMO-prevention	05/17/2002
	PMO-treatment	05/17/2002
Actonel with Calcium® (risedronate sodium and calcium carbonate, co-packaged) by Procter and Gamble		
35 mg oral tablets/week & 1,250 mg calcium carbonate (500 mg calcium equivalent)/day	PMO-prevention PMO-treatment	08/12/2005
Didronel® (etidronate disodium) by Procter and Gamble		
200 mg oral tablet or 400 mg oral tablet at 5-10 mg/kg/day < 6 months or 11-20 mg/kg/day < 3 months	Paget's disease	09/01/1977
Etidronate disodium by Genpharm		
200 or 400 mg oral tablet	Paget's disease	01/24/2003

§ PMO-postmenopausal osteoporosis; GIOP-Glucocorticoid-induced osteoporosis; OP/men-osteoporosis in men.
†Approval date by the U.S. Food and Drug Administration (FDA).
References: searchable Drug@FDA websites for FDA approved drug products, URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
HRT= hormone replacement therapy.

A review summarized the findings of some RCTs, and concluded that using HRT has a small protective effect on vertebral fractures but not on hip fractures.[164] However, the results of the Women Health Initiative (WHI) study, in which partial results were first released in 2002, changed the way that HRT has been used.[165, 166] In the WHI Study, which recruited 16,608 postmenopausal women who received 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate daily, a protective effect on fractures was found (RR =0.61, 95% CI 0.41-0.91 for hip fractures; RR =0.62, 95% CI 0.34-1.13 for vertebral fractures; RR =0.70, 95% CI 0.63-0.79 for total fractures), but the risks of stroke (RR =1.39, 95% CI 1.10-1.77) and total cardiovascular diseases (RR =1.12, 95% CI 1.01-1.24) were increased.[167, 168, 169] Although HRT showed a protective effect on osteoporotic fractures, its risks associated with other conditions outweighed the beneficial effects. Therefore, HRT is currently not recommended for the management of osteoporosis, and HRT should be used cautiously with appropriate monitoring.[170]

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164 Geusens, P. (2000). Hormonal replacement therapy in the prevention and treatment of glucocorticoid-induced osteoporosis. *Clinical and Experimental Rheumatology* 18(suppl. 21): S57-S59.

165 Kleerekoper, M. (2002). Lessons from the skeleton: was the Women's Health Initiative (WHI) a primary prevention trial? *Osteoporosis International* 13(9): 685-687.

166 Majumdar, S. R. *et al*. (2004). Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *Journal of the American Medical Association* 292(16): 1983-1988.

167 Anderson, G. L. *et al*. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 291(14): 1701-1712.

168 Manson, J. E. *et al*. (2003). Estrogen plus progestin and the risk of coronary heart disease. *New England Journal of Medicine* 349(6): 523-534.

169 Wassertheil-Smoller, S. *et al*. (2003). Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *Journal of the American Medical Association* 289(20): 2673-2684.

170 American College of Rheumatology (ACR) (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

In short, HRT was widely used for preventing bone loss at spine or reducing risks of vertebral fractures before 2002. The use of HRT for osteoporosis is not recommended given its risks for cardiovascular conditions. Other estrogen-related agents, the selective estrogen receptor modulators (SERMs), have fewer risks of adverse reactions compared to HRT. The SERMs are potentially used as anti-osteoporotic agents. The next section reviews the efficacy of SERMs on bone loss.

2.4.4 Selective Estrogen Receptor Modulators (SERMs)

Among Selective Estrogen Receptor Modulators (SERMs), only raloxifene has been evaluated and approved for the treatment of postmenopausal osteoporosis. Raloxifene (Evista@ by Eli Lilly) was approved by the FDA for the treatment of postmenopausal osteoporosis on December 9, 1997, and is available in 60 mg tablets. No published study of raloxifene for glucocorticoid-induced osteoporosis was found. Nevertheless, raloxifene may be used clinically as an intervention for glucocorticoid-induced osteoporosis in postmenopausal women. It may be helpful to review these raloxifene trials.

In a series of large double-blind RCTs, the Multiple Outcomes of Raloxifene Evaluation (MORE) study recruited 7,705 women diagnosed with postmenopausal osteoporosis and followed them for three years. A total of 2,576 women receiving raloxifene had significant reductions of the incidence of vertebral fracture (RR =0.7, 95% CI 0.5-0.8 for 60 mg; RR =0.5, 95% CI 0.4-0.7 for 100 mg) and had a protective effect on breast cancer (RR =0.1, 95% CI 0.04-0.24) but had an increased risk of endometrial

cancer (RR =3.1, 95% CI 1.5-6.2) compared with placebo control subjects.[171, 172] The prevention of vertebral fracture was supported in a recent meta-analysis (pooled RR =0.6, 95% CI 0.49-0.74).[173]

Raloxifene could be potentially useful in postmenopausal women for glucocorticoid-induced osteoporosis. However, more studies are needed to evaluate the relative risks of endometrial cancer from raloxifene use. Another type of anti-resorptive agent is calcitonin, and its efficacy is reviewed in the following section.

2.4.5 Calcitonin

Calcitonin is recommended as the second-line alternative for post-menopausal osteoporosis when other anti-osteoporosis medications are contraindicated.[174] Compared with calcium and vitamin D combination, calcitonin shows similar efficacy in increasing BMD or reducing risks of osteoporotic fractures in glucocorticoid users. In a two-year double-blind RCT recruiting 25 patients with temporal arteritis or polymyalgia, those who received 100 IU of salmon calcitonin had no significant difference in BMD values and incidence of vertebral fracture when compared with the control group who

171 Cummings, S. R. *et al*. (1999). The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *Journal of the American Medical Association* 281(23): 2189-2197.

172 Ettinger, B. *et al*. (1999). Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *Journal of the American Medical Association* 282(7): 637-645.

173 Seeman, E. *et al*. (2006). Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporosis International* 17(2): 313-316.

174 American College of Rheumatology (ACR) (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

took 1,500 mg of calcium and 400 IU of vitamin D supplements daily.[175] However, calcitonin is used clinically for managing pain caused by vertebral fractures. A meta-analysis concluded that calcitonin has a significant effect on relieving acute pain after recent vertebral fractures.[176] A recent systematic review of related RCTs supports the pain management effect of calcitonin.[177] The first salmon calcitonin product is Calcimar® (an injectable form by Rhone-Poulenc Rorer) which was approved by the FDA in 1975. Miacalcin® (salmon calcitonin by Novartis) is approved by the FDA only for postmenopausal women who cannot tolerate estrogen, or for whom estrogen is not an option. Miacalcin® is currently available in two forms: 200 IU/ml injection (approved on March 29, 1991) and 200 IU metered nasal spray (approved on August 17, 1995). Calcitonin-salmon recombinant (rDNA origin, Fortical® by Unigene) was approved for the treatment of postmenopausal osteoporosis on August 12, 2005, and is currently available as 200 IU metered nasal spray.

Anti-resorptive agents are widely used to treat glucocorticoid-induced osteoporosis as well as other types of osteoporosis. The efficacy of each anti-resorptive agent for glucocorticoid-induced osteoporosis varies; bisphosphonates showed the most promising results. Other treatments include anabolic agents which target the process of bone formation. The next section reviews the efficacy of anabolic agents for glucocorticoid-induced osteoporosis.

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175 Healey, J. H. *et al*. (1996). A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcified Tissue International* 58(2): 73-80.

176 Coyle, D. *et al*. (2001). Cost effectiveness of nasal calcitonin in postmenopausal women: use of Cochrane collaboration methods for meta-analysis within economic evaluation. *Pharmacoeconomics* 19(5): 565-575.

177 Knopp, J. *et al*. (2005). Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. *Osteoporosis International* 16(10): 1281-1290.

2.4.6 Anabolic Agents

Fluoride and parathyroid hormone are the two most common anabolic agents which have been evaluated for osteoporosis. In a two-year RCT recruiting 47 glucocorticoid users with established osteoporosis who received 500 mg of calcium per day, 0.2 mg of dihydrotachysterol per day and eight cycles of intermittent cyclical etidronate (one cycle =200 mg twice daily for 2 weeks and stop etidronate for 11 weeks), 23 patients receiving 25 mg of sodium fluoride twice daily had a significant increase in BMD at the spine (+8.9%, $p<0.01$) compared to 24 controls (placebo/etidronate); no significant change in BMD at hip nor in fracture rates was found between two groups.[178] Because the sample size of this study was relatively small, the efficacy of fluoride for glucocorticoid-induced osteoporosis is not conclusive.

The human parathyroid hormone 1-34 (hPTH 1-34) is a fragment of the intact parathyroid hormone 1-84. PTH (1-34) significantly increases BMD in the spine and hip in glucocorticoid users. In a one-year RCT recruiting women with postmenopausal osteoporosis who received glucocorticoid steroids, PTH (1-34) had a significant increase in BMD at the lumber spine within six months in comparison with those who received HRT.[179] The PTH treatment was discontinued six months after the initiation of therapy in this one-year trial. The effect of PTH on spine BMD remains for an additional year after the termination of therapy; however, the effect on hip BMD, which was not found

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178 Lems, W. F. *et al*. (1997). Is the addition of sodium fluoride to cyclical etidronate beneficial in the treatment of corticosteroid-induced osteoporosis? *Annals of Rheumatic Diseases* 56: 357-63.

179 Lane, N. E. *et al*. (1998). Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis: results of a randomized controlled clinical trial. *Journal of Clinical Investigation* 102(8): 1627-1633.

during the first six months of the treatment, appeared six months after the termination.[180, 181] This suggested that the onset time for PTH (1-34) effects on hip BMD may be relatively long. Teriparatide (Forteo[@] by Eli Lilly), a recombinant hPTH 1-34, was approved by the FDA for the treatment of postmenopausal osteoporosis on Nov 26, 2002, and is available in subcutaneous injection (0.25 mg/ml). Table 2.2 shows the dosing regimens, indications and approval dates for non-bisphosphonate agents.

Table 2.2 Dosing regimens, indications and approval dates for non-bisphosphonate agents

Brand name (generic name) and manufacturer		
Dosing regimen	**Indication‡**	**Approval date†**
Evista® (raloxifene hydrochloride) by Eli Lilly		
60 mg oral tablet/day	PMO-prevention	12/09/1997
	PMO-treatment	09/30/1999
Miacalcin® (calcitonin-salmon) by Novartis		
100 IU /ml injection	PMO-treatment	03/29/1991
200 IU/ml is discontinued		07/03/1986
200 IU/metered nasal spray/day		08/17/1995
Fortical® (calcitonin-salmon recombinant, rDNA origin) by Unigene		
200 IU/metered nasal spray/day Alternating nostrils daily	PMO-treatment	08/12/2005
Forteo® (teriparatide recombinant human, rDNA origin) by Lilly		
20 mcg/day subcutaneous injection into thigh or abdominal wall	PMO-treatment OP/men-treatment	11/26/2002

‡PMO-postmenopausal osteoporosis; OP/men-osteoporosis in men.
†Approval date by the U.S. Food and Drug Administration (FDA).
References: searchable Drug@FDA websites for FDA approved drug products, URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

180 Lane, N. E. *et al*. (2000). Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. *Journal of Bone and Mineral Research* 15(5): 944-951.

181 Lane, N. E. *et al*. (2000). Short-term increases in bone turnover markers predict parathyroid hormone-induced spinal bone mineral density gains in postmenopausal women with glucocorticoid-induced osteoporosis. *Osteoporosis International* 11(5): 434-442.

2.4.7 Combination Therapy

The efficacy of combination therapy for postmenopausal osteoporosis has been reviewed.[182] Combination therapy (e.g., BP-HRT, BP-raloxifene, calcitonin-HRT, PTH-HRT, etc.) generally shows increased BMD values and decreased risks of osteoporotic fractures when compared with monotherapy. Compared to monotherapy of BP or HRT, the BP-HRT combination shows reduced relative risks of osteoporotic fractures in an observational study.[183] However, the additive protective effects are generally small. Additionally, the chance of adverse reactions increases; adherence and tolerance are usually decreased. The benefit of using combination therapy may not outweigh potential adverse drug reactions; therefore, combination therapy is currently not recommended. More studies are needed to evaluate the efficacy, safety and adherence of combination therapy for osteoporosis in at least three areas: (1) exclusion of HRT as an option; (2) an adjustment of dose regimens for each option; and (3) an extended study period.

2.4.8 Effectiveness and Efficacy

In a cohort study using an electronic administrative and clinical database from a large health maintenance organization (HMO) plan covering 450,000 lives, a total of 3,031 glucocorticoid users were identified between 2000 and 2001, and 90% of the population were non-Hispanic white.[184] A total of 575 subjects were excluded because

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182 Compston, J. E. & Watts, N. B. (2002). Combination therapy for postmenopausal osteoporosis. *Clinical Endocrinology* 56(5): 565-569.

183 Tiller, W. (2004). Alendronate and hormone replacement therapy in the prevention of osteoporotic fracture: A pharmacoeconomic analysis employing a net-benefit regression method of cost-effectiveness. *Dissertation.* The University of Texas at Austin, Austin, TX, U.S. A.; 325 pages.

184 Feldstein, A. C. *et al*. (2005). Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. *Osteoporosis International* 16(12): 2168-2174.

of ineligibility of the HMO plan. Of 1,827 female glucocorticoid users, 46.4% received HRT and 18.3% received other anti-osteoporotic medications, including bisphosphonates, calcitonin and raloxifene. Of 1,204 male glucocorticoid users, 8.9% received either bisphosphonates or calcitonin.

Given the efficacy of anti-osteoporotic agents for glucocorticoid-induced osteoporosis, bisphosphonates are usually the first-line choice. However, bisphosphonates may not always be the best option for every patient. The "efficacy" of a medication shown in an RCT usually shows the ideal results among study subjects with relatively restricted criteria, so it usually does not reflect the "effectiveness" in patients who actually use that medication in the "real world." Combined with complex considerations (e.g., co-morbidities, social or economic issues), effectiveness is more meaningful to patients, healthcare providers, payers or policy makers than is efficacy.

2.4.8 Summary of Pharmacotherapy for Glucocorticoid-Induced Osteoporosis

This concludes the review of clinical outcomes of RCTs for glucocorticoid-induced osteoporosis. Calcium, vitamin D supplementation or the combination is the basic intervention for glucocorticoid-induced osteoporosis in most studies. Bisphosphonates showed the greatest efficacy for glucocorticoid-induced osteoporosis compared to other agents, so bisphosphonates are considered first-line agents. HRT was widely used as an intervention for osteoporosis, but is no longer recommended because of the risks of cardiovascular diseases. Instead, raloxifene may be the choice of postmenopausal women for managing osteoporosis, but more studies are needed to evaluate the risks of endometrial cancer. Calcitonin showed a relatively weak efficacy for osteoporosis, but it is used clinically for the management of pain associated

with vertebral fractures and it is the second-line agent. Teriparatide (PTH 1-34) is another potential agent for glucocorticoid-induced osteoporosis. The next section will focus on the evaluation of the economic burden of glucocorticoid-induced osteoporosis and its treatments, especially targeting cost-effectiveness studies.

2.5 ECONOMIC EVALUATIONS

Given limited resources, attention is focused on costs and utilization of medications. Cost-effectiveness analyses (CEA) can be helpful in addressing these issues because they integrate both economic and clinical outcomes, and compare the outcomes of potential alternatives with those of the reference (standard) treatment. Based on individual needs and information provided by the cost-effectiveness analyses, patients (along with their healthcare providers) may select the best approach to manage their conditions. The following two sections review the economic burden of glucocorticoid-induced osteoporosis and the cost-effectiveness of medications used for the prevention and/or the treatment of glucocorticoid-induced osteoporosis. It is noted that most studies included only direct medical costs.

2.5.1 Burden of Osteoporosis and Osteoporotic Fractures

Most studies of osteoporosis focused on osteoporotic vertebral and/or hip fractures. The vertebral fracture is the most common type, and the hip fracture usually accounts for the largest portion of the total direct and indirect medical costs. The estimated costs of osteoporosis or osteoporotic fractures vary in different settings and countries. No cost-of-illness or disease-burden study specifically targeting glucocorticoid users was found. However, the costs associated with all osteoporotic

fractures may give a hint of costs related to glucocorticoid-induced osteoporosis. Those studies conducted in European countries will be summarized first, followed by those in the U.S.

2.5.1.1 Hospital costs of osteoporotic fractures outside the U.S.

(1) Fractures at all sites. In Switzerland, the costs of hospitalizations for osteoporotic fractures in 2000 were $18,227 Swiss Francs (CHF) for hip fractures, $11,644 CHF for vertebral fractures and $6,260 CHF for forearm fractures,[185] or $10,356, $6,616 and $3,557 USD, respectively ($1 USD ≈ $1.76 CHF in 2000).[186] Of 62,535 hospitalized fractures, osteoporotic fractures accounted for 51% in women and 24% in men; about a half of all osteoporotic fractures involved the hip. In the U.K., the estimated direct medical costs of hip, spine, wrist and other osteoporotic fractures in women aged 50 years or more in 1998 were about £12,000, £479, £468 and £1,338 per fracture, respectively (in 1998 £),[187] or $19,800, $790, $772 and $2,208 USD (1£=$1.65 in 1998).[188].

(2) Hip fractures. The total inpatient cost for fractures at proximal humerus, distal radius/ulna and proximal hip in 2001 in France was estimated to range between €714 million and €762 million (2001 €),[189] or $643 and $656 million (€1 ≈ $0.90

185 Lippuner, K. *et al*. (2005). Epidemiology and direct medical costs of osteoporotic fractures in men and women in Switzerland. *Osteoporosis International* 16(Suppl 02): S8-S17.

186 URL: http://www.itu.int/aboutitu/annual_report/2000/financial_situation.html Accessed July 12, 2007.

187 Dolan, P. & Torgerson, D. J. (1998). The cost of treating osteoporosis fractures in the United Kingdom female population. *Osteoporosis International* 8(6): 611-617.

188 1£=$1.6120-1.7255 in 1998, URL: http://www.taxfreegold.co.uk/1998forexrates.html Accessed July 12, 2007.

189 Maravic, M. *et al*. (2005). Incidence and cost of osteoporotic fractures in France during 2001. a methodological approach by the national hospital database. *Osteoporosis International* 16(12): 1475-1480.

USD).[190] Another study reported that the total hospital costs for osteoporotic fractures in Sweden was about 351 million Swedish Kronors (SEK) in 1996[191] (or $52.4 million, 1 SEK=$0.1493 USD in 1996),[192] and that hip fractures accounted for 63% in men and 72% in women of the hospital admissions for osteoporotic fractures.

A survey recruiting 7,983 men and women aged 55 years or over in the Netherlands found that the estimated average incremental direct medical costs of hip fractures were about U.S. $10,000 within one year after fracture, and about an additional U.S. $1,000 in the second year, compared with matched participants without osteoporotic fractures in the study period (1990-1993).[193] These costs were not adjusted to the dollar values in the same year. It was also estimated in another study that the average cost per hip fracture in 2,374 Belgium patients aged 60 years or over in 1996 was U.S. $8,977 for the first year and U.S. $752 within one year after the fracture (1996 dollars).[194] In Belgium, the estimated direct medical cost of hospital stays for hip fracture among 159 female patients aged 50 years or more was €8,667, and its additional direct medical cost within one year after the fracture was €6,636 in 1996 (adjusted to 1998 €),[195] or $10,314 and $7,897, respectively (€1 ≈ $1.19 USD on January 4, 1999).[196]

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190 1Euro=$0.84-0.96 USD in 2001. URL: http://www.taxfreegold.co.uk/2001forexrates.html Accessed July 12, 2007.

191 Johnell, O. *et al*. (2005). The burden of hospitalised fractures in Sweden. *Osteoporosis International* 16(2): 222-228.

192 On average, $1 USD=6.7 SEK in 1996. URL: http://www.astrazeneca.com/sites/7/archive/Investors/Financial%20Reports/1995-1998/zeneca-1995-1997-basis-of-preparation.pdf Accessed July 12, 2007.

193 De Laet, C. E. D. H. *et al*. (1999). Incremental cost of medical care after hip fracture and first vertebral fracture: the Rotterdam study. *Osteoporosis International* 10(1): 66-72.

194 Reginster, J.-Y. *et al*. (1999). Direct costs of hip fractures in patients over 60 years of age in Belgium. *Pharmacoeconomics* 15(5): 507-514.

195 Autier, P. *et al*. (2000). Costs induced by hip fractures: a prospective controlled study in Belgium. *Osteoporosis International* 11(5): 373-380.

196 $1 USD =0.84219 Euro, as of Jan. 4, 1999. URL: http://www.geocities.com/eureka/concourse/8751/tabl-er2.htm Accessed July 12, 2007.

(3) Vertebral fractures. A study surveyed the Ministries and Departments of Health in 15 European countries, and found that the total hospital cost of osteoporotic vertebral fractures for patients aged over 50 years in these countries was about €377 million per year (average €3,892 per fracture, 2001 €), or 339 million per year and average $3,505 per fracture (€1≈ $0.90 USD),[197] which was 63% of the average cost per hip fracture (€6,178 or $5,560 USD).[198]

2.5.1.2 Direct and indirect costs of osteoporotic fractures outside the U.S.

In Sweden, the estimated (direct and indirect combined) costs of vertebral, hip and wrist fractures within one year after the fracture among 635 male and female patients aged 50 years or more were €12,544, €14,221 and €2,147 (2004 €), [199] respectively, or $16,558, $18,772 and $2,834, respectively (€1≈ $1.32 USD in 2004).[200] The indirect costs include opportunity cost (work loss per day), and costs for special living arrangements (e.g., nursing home, group living, home help), transportation and informal care (value of lost leisure time).

2.5.1.3 Direct medical costs of osteoporotic fractures in the U.S.

Four studies were found for estimation of costs of fractures in the U.S. In California, the 1998 Medicare expenditure for the direct medical costs of osteoporosis

197 1Euro=$0.84-0.96 USD in 2001. URL: http://www.taxfreegold.co.uk/2001forexrates.html Accessed July 12, 2007.

198 Finnern, H. W. & Sykes, D. P. (2003). The hospital cost of vertebral fractures in the EU: estimates using national datasets. *Osteoporosis International* 14(5): 429-436.

199 Borgstrom, F. *et al*. (2006). Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporosis International 17(5): 637-650.

200 1 Euro=$1.32 in December 2004. URL: http://www.molon.de/travelogues/Singapore/2004/#Money Accessed July 12, 2007.

and related conditions was over $2.4 billion; 59% of which was for nursing home care.[201] In 600 women aged 45 years or more who enrolled in a U.S. health maintenance organization (HMO) between 1998 and 1999, the total direct medical cost for osteoporosis or osteoporotic fractures was $411,684 (average $686 per person).[202] The disease-specific costs were $645 per patient per year (PPPY) for osteoporosis and $939 PPPY for osteoporotic fractures. The estimated cost (including inpatient, outpatient and long-term care) in Florida was over $1.2 billion for 86,428 osteoporotic fractures in 2000, and it was projected to reach $2.1 billion for 151,622 osteoporotic fractures in 2025.[203] The direct medical costs of follow-ups after osteoporotic fractures were reported. The median incremental costs of hip, vertebral and wrist fractures in one year after fracture were $10,338, $1,255 and $1,496, respectively (1995 dollars) in 1,263 Minnesota patients aged 50 years or more.[204]

Trends for costs of osteoporotic fractures

Table 2.3 summarizes direct medical costs of osteoporotic fractures reported in previous studies. Regardless of region, the economic burden of osteoporosis or osteoporotic fractures is significant. The burden of osteoporotic fractures is mostly due to the hospital costs. The first-year expense for hip fractures is about $10,000 per patient, and it accounts for the largest portion of direct medical expenses for osteoporotic fractures. Although there is no information on costs of glucocorticoid-induced

201 Max, W. *et al*. (2002). The burden of osteoporosis in California, 1998. *Osteoporosis International* 13(6): 493-500.

202 Desai, S. S. *et al*. (2003). The cost of treating osteoporosis in a managed health care organization. *Journal of Managed Care Pharmacy* 9(2): 142-149.

203 Burge, R. T. *et al*. (2003). Methodology for estimating current and future burden of osteoporosis in state populations: application to Florida in 2000 through 2025. *Value in Health* 6(5): 574-583.

204 Gabriel, S. E. *et al*. (2002). Direct medical costs attributable to osteoporosis fractures. *Osteoporosis International* 13(4): 323-330.

osteoporosis and osteoporotic fractures, the burden of osteoporosis and osteoporotic fractures in glucocorticoid users may be significant, if glucocorticoid-induced bone loss is left untreated. Osteoporosis and osteoporotic fractures need to be managed from the perspectives of both clinical and economic considerations. The next question is: What is the most cost effective option to manage glucocorticoid-induced osteoporosis? The following section summarizes some findings from the CEAs, which may help answer this question.

2.5.2 Costs and Effectiveness of Agents for Glucocorticoid-Induced Osteoporosis

Most outcomes research for anti-osteoporotic agents in the literature focused on management of postmenopausal osteoporosis. Two articles were found to review cost-effectiveness, cost-utility and cost-minimization analyses of anti-osteoporotic treatments in the literature. Cranney, Coyle and colleagues reviewed 19 cost-effectiveness studies from 1983 to 1998,[205, 206] and Fleurence *et al.* provided a review of 42 studies which were published by December 2004.[207] A total of 71% of the 42 studies in Fleurence's review were conducted in Sweden, the U.K. or the U.S.; 88% included females only; 38% addressed hip fracture only; and the major intervention groups were HRT (27%), bisphosphonates (17%) and calcium and/or vitamin D (16%). As indicated previously, research in postmenopausal osteoporosis may not be applicable to research in glucocorticoid-induced osteoporosis.

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205 Cranney, A. *et al*. (1999). A review of economic evaluation in osteoporosis. *Arthritis Care and Research* 12(6): 425-434.

206 Coyle, D. *et al*. (2000). Cost-effectiveness research in osteoporosis. *Drug Development Research* 49(3): 135-140.

207 Fleurence, R. L. *et al*. (2006). Economic evaluations of interventions for the prevention and treatment of osteoporosis: a structured review of the literature. *Osteoporosis International* 17(1): 29-40.

Table 2.3 Direct medical costs of osteoporotic fractures reported by previous studies

Study	Country	Data sources, year	Subjects	Fracture type	Cost (Original)†	Cost (2005 US$)§
Lippuner *et al.*[a]	Switzerland	Administrative & medical claims, 2000	62,535 hospitalized men & women	hip spine forearm	$18,227 CHF $11,644 CHF $6,260 CHF	$13,108 $8,374 $4,502
Dolan & Torgerson[b]	U.K.	Census data & surveys & national databases, 1998	women ≧ 50 years old	hip spine forearm	£12,000 £479 £468	$27,012 $1,078 $1,053
De Laet *et al.*[c]	Netherlands	Survey, 1990-1993	7,983 men & women ≧ 55 years old	hip	$10,000 (1st yr) + $1,000 /yr	$15,500 (1st yr) + $1,550 /yr
Reginster *et al.*[d]	Belgium	National databases, 1996	2,374 hospitalized men & women ≧ 60 years old	hip	$8,977 (1st yr) + $752 /yr	$13,005 (1st yr) + $1,089 /yr
Autier *et al.*[e]	Belgium	1-year perspective study, 1995-1996	170 hospitalized women ≧ 50 years old	hip	€8,667	$13,613
Finnern & Sykes[f]	15 European countries	Surveys on Ministries of Health, national statistics, 2001	men & women ≧ 50 years old	hip spine	€6,178 €3,892	$6,715 $4,233
Desai *et al.*[g]	U.S.	HMO Claims data, 1998-1999	600 women ≧ 45 years old	all	$939 /yr	$1,281 /yr
Gabriel *et al.*[h]	U.S.	Mayo database, 1995	1,263 men & women ≧ 50 years old	hip spine forearm	$10,338 (1st yr) $1,255 (1st yr) $1,496 (1st yr)	$15,050 (1st yr) $1,818 (1st yr) $2,167 (1st yr)

HMO=health maintenance organization; yr=year
† CHF=Swiss Francs; £ =UK Pound; €=Euro
§ Converted to 2005 USD based on average foreign exchange rates at that year and U.S. Consumer Price Index (CPI) medical component;
a. Lippuner *et al.* (2005). *Osteoporosis International* 16(Suppl 02): S8-S17.
b. Dolan & Torgerson (1998). *Osteoporosis International* 8(6): 611-617.
c. De Laet *et al*. (1999). *Osteoporosis International* 10(1): 66-72.
d. Reginster *et al*. (1999). *Pharmacoeconomics* 15(5): 507-514.
e. Autier *et al*. (2000). *Osteoporosis International* 11(5): 373-380.
f. Finnern. & Sykes. (2003). *Osteoporosis International* 14(5): 429-436.
g. Desai *et al*. (2003). *Journal of Managed Care Pharmacy* 9(2): 142-149.
h. Gabriel *et al*. (2002). *Osteoporosis International* 13(4): 323-330.

Three cost-effectiveness studies were found in the literature to compare long-term outcomes of treatment options for glucocorticoid-induced osteoporosis. Long-term outcomes of anti-osteoporotic treatments were estimated by Markov models in these three studies. The first study was presented as a poster on November 11, 1998 at the annual meeting of the American College of Rheumatology.[208] Homik *et al.* modeled the 10-year cost-effectiveness of bisphosphonates in the prevention of glucocorticoid-induced osteoporosis for hypothetical young women treated with glucocorticoid steroids. The reported annual costs per patient for "no prophylaxis," "conditional prophylaxis" and "universal prophylaxis" were $75, $170 and $780, respectively. Compared with "no prophylaxis," the incremental costs per vertebral fracture avoided were $2,000 for "conditional prophylaxis" and $9,000 for "universal prophylaxis."

The second study was conducted by Solomon and Kuntz who used a Markov model with simulations to estimate the long-term costs and quality-adjusted life years (QALYs) of three strategies involving alendronate use in the prevention of glucocorticoid-induced osteoporosis.[209] The three strategies were "watchful waiting" (no screening, treated only when a fracture occurs), "screen and treat" (screening but treated only when the T-score of BMD is below -1.0) and "treat all" (treated without any screening). The hypothetical cohorts were postmenopausal women aged 55 who were diagnosed with rheumatoid arthritis and about to initiate glucocorticoid therapy. Compared to the "watchful waiting" group, the incremental cost per QALY gained was

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208 Homik, J. E. *et al*. (1998). Cost-effectiveness of bisphosphonates in the prevention of corticosteroid-induced osteoporosis. *Arthritis and Rheumatism* 4(Suppl. 9): S303.

209 Solomon, D. H. & Kuntz, K. M. (2000). Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. *Arthritis and Rheumatism* 43(9): 1967-1975.

$93,150 for the "screen and treat" group and $100,000 for the "treat all" group. The authors indicated that the results of modeling were still limited because the model used the efficacy data derived from the literature with few studies specifically targeting glucocorticoid users. In a study for postmenopausal osteoporosis, for example, a range of $18,000 to $77,000 per quality adjusted life year (QALY) gained was reported to detect prevalent vertebral deformity in osteopenic postmenopausal women receiving alendronate therapy compared to no drug therapy..[210]

The third study was conducted by Buckley and Hillner who used a Markov model to estimate the 10-year and lifetime costs and effectiveness of calcium and vitamin D supplements, cyclic etidronate, and alendronate in the prevention of vertebral fractures among four hypothetical cohorts of Caucasian women receiving one-year glucocorticoid therapy..[211] The cohorts were 30-year-old women with normal BMD (T-score =0), 50-year-old women with borderline bone loss (T-score =-1), 60-year-old women with moderate bone loss (T-score =-1.5) and 70-year-old women with severe bone loss (T-score =-2). The incremental costs per vertebral fracture avoided ranged from $800 to $8,923 (10-year) or $800 to $1,944 (lifetime) for etidronate treatment, and ranged from $2,318 to $25,429 (10-year) or $2,318 to $2,728 (lifetime) for alendronate treatment compared to calcium/vitamin D treatment. The combination of calcium and vitamin D supplements was the most cost-effective option for most comparisons.

Table 2.4 summarizes important results of these three cost-effectiveness analyses of bisphosphonate treatment for prevention of glucocorticoid-induced osteoporosis.

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210 Schousbue, J. T. *et al*. (2006). Cost-effectiveness of vertebral fracture assessment to detect prevalent vertebral deformity and select postmenopausal women with a femoral neck T-score>-2.5 for alendronate therapy: a modeling study. *Journal of Clinical Densitomatry* 9(2): 133-143.

211 Buckley, L.M. & Hillner, B. E. (2003). A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *Journal of Rheumatology* 2003 30(1): 132-138.

Subjects of these studies were hypothetical women, and long-term estimations were based on Markov modeling. The cost-effectiveness (CE) ratios of comparisons provide limited information for the management of glucocorticoid-induced osteoporosis. Compared to no treatment, Buckley *et al.* estimated a range of $838 to $121,125 and Homik *et al.* reported a range of $2,000 to $9,000 as the incremental costs per vertebral fracture avoided for bisphosphonate therapy in glucocorticoid users; Solomon *et al.* reported a range of $93,150 to $100,000 as the incremental cost per QALY gained for bisphosphonates in glucocorticoid users. Some studies suggested that interventions should be implemented in glucocorticoid users for preventing or treating bone loss. Nevertheless, physicians seem reluctant to prescribe them. The next section elaborates on some barriers to glucocorticoid-induced osteoporosis management in daily practice.

Table 2.4 Previous cost-effectiveness studies of bisphosphonate treatments for prevention of glucocorticoid-induced osteoporosis

Study	Subject	Reference group	Treatment group	ICER (10 year)	ICER (lifetime)
Homik *et al*.[a]	Hypothetical young women	no prophylaxis	conditional prophylaxis	$2,000[d]	-
			universal prophylaxis	$9,000[d]	-
Solomon & Kuntz[b]	Hypothetical 55 y/o women with RA	watchful waiting	screen & treat	$93,150[e]	
			Treat all	$100,000[e]	
Buckley & Hillner[c]	Hypothetical 30 y/o women BMD T score=0	Calcium + vit D	Etidronate	-	$1,944[d]
			Alendronate	-	$2,728[d]
	Hypothetical 50 y/o women BMD T score=-1		Etidronate	$8,923[d]	$1,563[d]
			Alendronate	$25,429[d]	$2,632[d]
	Hypothetical 60 y/o women BMD T score=-1.5		Etidronate	$7,281[d]	$1,169[d]
			Alendronate	$14,000[d]	$2,826[d]
	Hypothetical 70 y/o women BMD T score=-2		Etidronate	$800[d]	$800[d]
			Alendronate	$2,318[d]	$2,318[d]

ICER=incremental cost-effectiveness ratio; RA=rheumatoid arthiritis; y/o=years old;

a. Homik *et al*. (1998). *Arthritis and Rheumatism* 4(Suppl. 9): S303.

b. "watchful waiting" (no screening, treated only when a fracture occurs), "screen & treat" (screening but treated only when the T-score of BMD is below -1.0), "treat all" (treated without any screening); Solomon & Kuntz (2000). *Arthritis and Rheumatism* 43(9): 1967-1975.

c. ICERs were recalculated by using calcium/vit D as the reference group from tables in this reference. Buckley & Hillner (2003). *Journal of Rheumatology* 30(1): 132-138.

d. Cost per vertebral fracture avoided.

e. Cost per quality-adjusted life year (QALY) gained.

2.6 BARRIERS TO THE MANAGEMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoid-induced osteoporosis is undertreated. A relatively low percentage of glucocorticoid users receive proper interventions for glucocorticoid-induced osteoporosis. A population-based, retrospective study of British patients in general practices indicated that only 14% (41/303) of long-term (for at least 3 months) oral glucocorticoid users aged 12-94 years had received preventive medication in the past four years.[212] A total of 244,235 adult glucocorticoid users who registered with the U.K. General Practice Research Database (GPRD) before December 1997 received at least one oral glucocorticoid prescription (mean =6.8 prescriptions, median =2 prescriptions); about 4% to 5.5% of them used calcium/vitamin D, bisphosphonates, estrogens or calcitonin during oral glucocorticoid therapy.[213] Of 215 adult outpatients who had received at least 5 mg of prednisone (or its equivalent) daily for at least one month at the San Francisco General Hospital from March 1996 to February 1997, 58% also received calcium, vitamin D, calcium/vitamin D combination or HRT.[214] In a prospective study conducted in a district general hospital in the U.K. from January to September of 1999, 92 glucocorticoid users were identified and 51 of them were qualified for the prevention of glucocorticoid-induced osteoporosis.[215] Of these 51 inpatients, 18 (35.3%) received effective prophylaxis for glucocorticoid-induced osteoporosis (11 with bisphosphonates, seven with HRT), 10 received inadequate prophylaxis (five with calcium only, two with vitamin D only and three with calcium/vitamin D combination);

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212 Walsh, L. J. *et al*. (1996). Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *British Medical Journal* 313(7053): 344-346.

213 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

214 Aagaard, E. M. *et al*. (1999). Prevention of glucocorticoid-induced osteoporosis: provider practice at an urban county hospital. *American Journal of Medicine* 107(5): 456-460.

215 Hart, S. R. & Green, B. (2002). Osteoporosis prophylaxis during corticosteroid treatment: failure to prescribe. *Postgraduate Medical Journal* 78(918): 242-243.

three had previously used bisphosphonates but discontinued (due to poor compliance or intolerance) without taking another anti-osteoporotic agent; and 20 did not have any treatment for glucocorticoid-induced osteoporosis.

Patients with osteoporotic fractures are also undertreated for further bone loss in general. A study which surveyed hip fracture patients aged 65 or more in Canada showed that only 81 of 356 patients (23%) were treated with bisphosphonates, HRT, calcitonin or vitamin D_3 after fractures.[216] Bisphosphonates include alendronate and etidronate; risedronate was not available during the study. Among these 81 patients, 74 received bisphosphonates and 12 received HRT; 10 females received two different types of anti-osteoporotic agents during the post-fracture period; one female received three different drugs; and none received SERMs.

The pattern of prevention also varies with different types of clinicians. For example, rheumatologists and pulmonologists were more likely to prescribe medications for prevention of glucocorticoid-induced osteoporosis in comparison with other specialists. Compared to internists, the odds ratios (ORs) of performing screenings for osteoporosis were 0.49 (95% CI 0.28-0.86) for gastroenterologists, 0.56 (95% CI 0.30-1.04) for primary care physicians and 1.48 (95% CI 1.06-2.08) for rheumatologists in a study of 6,281 glucocorticoid users.[217] Few gastrointestinal conditions require long-term glucocorticoid therapy, so gastroenterologists are less likely to screen for osteoporosis. Many rheumatic diseases require chronic glucocorticoid therapy, so rheumatologists are more likely to order a check of bone mass.

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216 Cree, M. W. *et al*. (2003). Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteoporosis International* 14(9): 722-727.

217 Curtis, J. R. *et al*. (2005). Longitudinal patterns in the prevention of osteoporosis in glucocorticoid-treated patients. *Arthritis and Rheumatism* 52(8): 2485-2494.

Some possible reasons have been noted in the literature for the insufficient treatment of glucocorticoid-induced osteoporosis: (1) physicians may not be convinced of the clinical importance of GIOP management; (2) the risk factors for different subgroups (gender, age, etc.) are unclear; and (3) there is a lack of supportive evidence for the efficacy or selection of therapeutic agents.[218] Potential barriers to the treatment of postmenopausal osteoporosis were also noted: (1) "virtually silent" symptoms for osteoporosis; (2) lack of acceptance of the therapy; and (3) lack of adherence to long-term therapy for osteoporosis.[219] These points may be applicable to the management of glucocorticoid-induced osteoporosis. From the perspective of primary care practice, the barriers to management of glucocorticoid-induced osteoporosis include: (1) the chance of developing glucocorticoid-induced osteoporosis or related osteoporotic fractures is relatively low in the general population; (2) not all individuals at risk develop osteoporosis; it is difficult to identify individual patients at risk; (3) even if osteoporosis and osteoporotic fractures occur, osteoporosis and vertebral fractures are silent unless there are symptomatic presentations (e.g., reduced height, back pain). Therefore, some physicians are not convinced of the need for prevention of glucocorticoid-induced osteoporosis.

Additionally, even if interventions are provided, bone loss cannot be completely recovered. Many interventions effectively increase bone mineral density (BMD), but a patient's BMD usually does not reach the original level. Although the risk of osteoporotic fractures is decreased after interventions, some patients still develop osteoporotic fractures. For example, 18 out of 38 patients who had received

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218 Bijlsma, J. W. J. (1997). Prevention of glucocorticoid induced osteoporosis. *Annals of the Rheumatic Diseases* 56(9): 507-509.

219 Cuddihy, M. T. (2003). Barriers to postfracture osteoporosis care in postmenopausal women: challenges and opportunities. *Journal of General Internal Medicine* 18(1): 70-71.

bisphosphonates, HRT, calcitonin or vitamin D_3 (prior to fracture) still developed hip fractures in the study surveying 449 hip fracture patients aged 65 or more in Canada.[220] However, the dosage regimens and duration of the therapy were not reported in this study; it is unclear whether proper interventions were selected for these patients.

Compliance and tolerance are important issues to be considered when long-term therapy for osteoporosis is planned. Patients who receive long-term glucocorticoid therapy also require long-term interventions for preventing further glucocorticoid-induced bone loss. The selection of the best therapy for glucocorticoid-induced osteoporosis should consider patients' acceptance. If compliance is low, then the therapeutic effects are reduced. Low compliance may result from side effects of anti-osteoporosis therapy.

Moreover, patients may have unequal access to care. Even if patients have access to care, their willingness to pay for long-term, costly treatments varies. All of the above reasons result in under-diagnosis and under-treatment of glucocorticoid-induced osteoporosis and related osteoporotic fractures. Therefore, there is a need for studies which address these concerns and provide information regarding the management of glucocorticoid-induced osteoporosis. The next section lists some of the areas that have not been addressed in the literature.

2.7 GAPS IN THE LITERATURE AND POSSIBLE RESEARCH QUESTIONS

Four missing pieces of information in the literature are identified. First, the prevalence and incidence of glucocorticoid-induced osteoporosis and glucocorticoid-induced osteoporotic fractures in the U.S. have not been estimated.

220 Cree, M. W. *et al*. (2003). Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteoporosis International* 14(9): 722-727.

More epidemiologic information allows for more accurate estimations of risks and economic burden of glucocorticoid-induced osteoporosis and glucocorticoid-induced osteoporotic fractures. To estimate the prevalence and incidence rates in the U.S., the population at risk must be described. No national estimates are currently available regarding background characteristics of glucocorticoid users in the U.S. Some important characteristics (such as gender, age and glucocorticoid user) which may have an impact on outcomes should be assessed.

The second missing piece of information in the literature is "real-world" outcomes of anti-osteoporotic treatments in glucocorticoid users. Information regarding effectiveness (i.e., "real-world" use) of anti-osteoporotic agents is usually more meaningful than "ideal" drug efficacy data. Although published studies have shown efficacy and effectiveness data for each therapeutic option for osteoporosis, most studies were not specifically designed for glucocorticoid users. Therefore, results from these studies may not be applicable to glucocorticoid users. Even if some studies targeted glucocorticoid users, there are many limitations including small sample sizes (which limits the study power), short observation periods for anti-osteoporosis interventions, and confounding issues (including underlying conditions). Additionally, differences in study criteria may generate unfair comparisons across studies. A study simultaneously comparing therapeutic options for glucocorticoid-induced osteoporosis is needed. Furthermore, glucocorticoid-induced bone loss may occur within three months, so there is a need for cost-effectiveness analyses to evaluate "short-term," "real-world" outcomes of anti-osteoporotic agents.

The third missing piece of information in the literature is long-term outcomes of anti-osteoporotic treatments in glucocorticoid users Long-term glucocorticoid users require long-term preventive treatments to decrease the risk of glucocorticoid-induced

bone loss. There is a need to evaluate long-term outcomes of these preventive treatments in glucocorticoid users. No study was found to measure long-term outcomes of anti-osteoporotic treatments in glucocorticoid users. Three studies used modeling techniques to estimate long-term outcomes related to osteoporosis and fractures for glucocorticoid users. However, as described previously, the inputs of Markov models in these studies were derived from efficacy data instead of effectiveness data. Use of effectiveness data as model inputs should yield long-term estimates which more likely reflect the real long-term outcomes.

The fourth missing piece of information in the literature is the lack of comparisons among all anti-osteoporotic treatments for glucocorticoid users simultaneously. It is difficult to synthesize study results and compare outcomes of anti-osteoporotic treatments across different studies which have different sets of study criteria, methodology and populations at risk. A study is needed to make a fair comparison of outcomes among all anti-osteoporotic treatments for glucocorticoid users.

These pieces of information, which include both short-term and long-term "real-world" cost-effectiveness outcomes of anti-osteoporotic treatments, will assist the decision-makers in selecting strategies which may manage glucocorticoid-induced osteoporosis and fractures in glucocorticoid users in a more proper way. There is a need for a study which integrates all pieces of information, and provides an overall recommendation.

- **Research Questions**

The following six research questions address issues relating to the above gaps in the literature. The long-term users of oral glucocorticoid tablets in the U.S. were the main focus of this study. Anti-osteoporotic treatments considered in this study include bisphosphosnates, calcitonin, hormone replacement therapy (HRT), raloxifene, the combination of HRT and bisphosphonates, teriparatide and no treatment.

(1) How were anti-osteoporotic agents used in glucocorticoid users in the U.S.? What are the characteristics of these users? In order to make a fair comparison, can some confounding factors, which may have an impact on study outcomes, be explained or measured, or at least be partially controlled?

(2) What are the prevalence and incidence rates of glucocorticoid-induced osteoporosis and related osteoporotic fractures in glucocorticoid users in the U.S.?

(3) What are the average direct medical costs for evaluation of osteoporosis and for treatment of osteoporotic fractures in glucocorticoid users in the U.S.?

(4) What are the average direct medical costs associated with anti-osteoporotic treatments in glucocorticoid users in the U.S.?

(5) What are the long-term estimates of costs and osteoporotic fracture rates based on actual data from glucocorticoid users who used anti-osteoporotic agents and for those who did not?

(6) What is the most cost-effective option among anti-osteoporotic treatments for the prevention of glucocorticoid-induced fractures for glucocorticoid users in the U.S.? The next sections describe the study goals, objectives and hypotheses which address these research questions.

2.8 STUDY OBJECTIVES

Six study objectives were established to match the six research questions. These study objectives are:

(1) To describe and compare background characteristics of oral glucocorticoid tablet users using different anti-osteoporotic treatments in the U.S. Anti-osteoporotic treatments include bisphosphonate therapy (BP), calcitonin therapy (CN), hormone replacement therapy (HT), a combination of HT & BP (HB), raloxifene therapy (RF) and "watching and waiting" strategy (control group, CT). These characteristics include gender, age and glucocorticoid use;

(2) To estimate the national annual prevalence and incidence rates of glucocorticoid-induced osteoporosis and related fractures in oral glucocorticoid tablet users in the U.S.;

(3) To estimate national average direct medical costs associated with evaluation of osteoporosis and treatments of osteoporotic fractures in oral glucocorticoid tablet users in the U.S.;

(4) To estimate and compare national average direct medical costs associated with preventive anti-osteoporotic treatments in oral glucocorticoid tablet users in the U.S.;

(5) To develop a Markov model that projects two-year, 10-year and lifetime estimates of costs and effectiveness of anti-osteoporotic treatments for oral glucocorticoid tablet users in the U.S.; and

(6) To suggest the best cost-effective option for the prevention and management of glucocorticoid-induced fractures in oral glucocorticoid tablet users in the U.S.

2.9 STUDY HYPOTHESES

This section describes the hypotheses that were developed for four of the six study objectives. Study subjects were categorized into subgroups by gender, type of glucocorticoid use, and type of anti-osteoporotic treatments. Two types of glucocorticoid use include long-term glucocorticoid use (LTGS) for subjects who received oral glucocorticoid tablets for a minimal period of 90 days, and high-risk glucocorticoid use (HRGS) for subjects who received a minimal cumulative dose of 450 mg of oral prednisone tablets (or its equivalent). It is noted that LTGS and HRGS are not mutually exclusive to each other; some subjects are categorized into both types. Anti-osteoporotic treatments include bisphosphonate therapy (BP), calcitonin therapy (CN), hormone replacement therapy (HT), a combination of HT & BP (HB), raloxifene therapy (RF) and "watching and waiting" strategy (control group, CT). Four sets of hypotheses are described in detail as follows.

2.9.1 Hypotheses for Objective One

Average ages, average cumulative glucocorticoid doses, average cumulative quantity of glucocorticoid tablets and average glucocorticoid doses per tablet are compared among subgroups. The hypotheses for the first objective are:

- **Average age**

Ho_{1A1}: $Age_{LTGS\text{-}F(BP)} = Age_{LTGS\text{-}F(CN)} = Age_{LTGS\text{-}F(HB)} = Age_{LTGS\text{-}F(HT)} = Age_{LTGS\text{-}F(RF)} = Age_{CTL\text{-}F}$

There is no significant difference in average ages among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1A2}: $Age_{LTGS\text{-}M(BP)} = Age_{LTGS\text{-}M(CN)} = Age_{CTL\text{-}M}$

There is no significant difference in average ages among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1A3}: $Age_{HRGS\text{-}F(BP)} = Age_{HRGS\text{-}F(CN)} = Age_{HRGS\text{-}F(HB)} = Age_{HRGS\text{-}F(HT)} = Age_{HRGS\text{-}F(RF)} = Age_{CTL\text{-}F}$

There is no significant difference in average ages among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

Ho_{1A4}: $Age_{HRGS\text{-}M(BP)} = Age_{HRGS\text{-}M(CN)} = Age_{CTL\text{-}M}$

There is no significant difference in average ages among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

- **Average cumulative glucocorticoid dose (CGSD)**

Ho_{1B1}: $CGSD_{LTGS\text{-}F(BP)} = CGSD_{LTGS\text{-}F(CN)} = CGSD_{LTGS\text{-}F(HB)} = CGSD_{LTGS\text{-}F(HT)} = CGSD_{LTGS\text{-}F(RF)} = CGSD_{CTL\text{-}F}$

There is no significant difference in average cumulative glucocorticoid doses (CGSD) among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1B2}: $CGSD_{LTGS\text{-}M(BP)} = CGSD_{LTGS\text{-}M(CN)} = CGSD_{CTL\text{-}M}$

There is no significant difference in average cumulative glucocorticoid doses (CGSD) among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1B3}: $CGSD_{HRGS\text{-}F(BP)} = CGSD_{HRGS\text{-}F(CN)} = CGSD_{HRGS\text{-}F(HB)} = CGSD_{HRGS\text{-}F(HT)} = CGSD_{HRGS\text{-}F(RF)} = CGSD_{CTL\text{-}F}$

There is no significant difference in average cumulative glucocorticoid doses (CGSD) among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

Ho_{1B4}: $CGSD_{HRGS\text{-}M(BP)} = CGSD_{HRGS\text{-}M(CN)} = CGSD_{CTL\text{-}M}$

There is no significant difference in average cumulative glucocorticoid doses (CGSD) among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

- **Average cumulative quantity of oral glucocorticoid tablets (CGSQ)**

Ho_{1C1}: $CGSQ_{LTGS\text{-}F(BP)} = CGSQ_{LTGS\text{-}F(CN)} = CGSQ_{LTGS\text{-}F(HB)} = CGSQ_{LTGS\text{-}F(HT)} = CGSQ_{LTGS\text{-}F(RF)} = CGSQ_{CTL\text{-}F}$

There is no significant difference in average cumulative quantity of oral glucocorticoid tablets (CGSQ) among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1C2}: $CGSQ_{LTGS\text{-}M(BP)} = CGSQ_{LTGS\text{-}M(CN)} = CGSQ_{CTL\text{-}M}$

There is no significant difference in average cumulative quantity of oral glucocorticoid tablets (CGSQ) among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1C3}: $CGSQ_{HRGS\text{-}F(BP)} = CGSQ_{HRGS\text{-}F(CN)} = CGSQ_{HRGS\text{-}F(HB)} = CGSQ_{HRGS\text{-}F(HT)} = CGSQ_{HRGS\text{-}F(RF)} = CGSQ_{CTL\text{-}F}$

There is no significant difference in average cumulative quantity of oral glucocorticoid tablets (CGSQ) among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

Ho_{1C4}: $CGSQ_{HRGS\text{-}M(BP)} = CGSQ_{HRGS\text{-}M(CN)} = CGSQ_{CTL\text{-}M}$

There is no significant difference in average cumulative quantity of oral glucocorticoid tablets (CGSQ) among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

- **Average glucocorticoid dose per tablet (DGSD)**

Ho_{1D1}: $DGSD_{LTGS\text{-}F(BP)} = DGSD_{LTGS\text{-}F(CN)} = DGSD_{LTGS\text{-}F(HB)} = DGSD_{LTGS\text{-}F(HT)} = DGSD_{LTGS\text{-}F(RF)} = DGSD_{CTL\text{-}F}$

There is no significant difference in average glucocorticoid dose per tablet (DGSD) among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1D2}: $DGSD_{LTGS\text{-}M(BP)} = DGSD_{LTGS\text{-}M(CN)} = DGSD_{CTL\text{-}M}$

There is no significant difference in average glucocorticoid dose per tablet (DGSD) among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.

Ho_{1D3}: $DGSD_{HRGS\text{-}F(BP)} = DGSD_{HRGS\text{-}F(CN)} = DGSD_{HRGS\text{-}F(HB)} = DGSD_{HRGS\text{-}F(HT)} = DGSD_{HRGS\text{-}F(RF)} = DGSD_{CTL\text{-}F}$

There is no significant difference in average glucocorticoid dose per tablet (DGSD) among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

Ho_{1D4}: $DGSD_{HRGS\text{-}M(BP)} = DGSD_{HRGS\text{-}M(CN)} = DGSD_{CTL\text{-}M}$

There is no significant difference in average glucocorticoid dose per tablet (DGSD) among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.

2.9.2 Hypotheses for Objective Two

Annual prevalence and incidence rates of glucocorticoid-induced osteoporosis and related fractures in glucocorticoid tablet users in the U.S. are estimated. These rates are separately calculated for men and women and for long-term glucocorticoid users (LTGS) and high-risk glucocorticoid users (HRGS). However, no hypothesis is needed for the second objective.

2.9.3 Hypotheses for Objective Three

Average direct medical costs associated with evaluation of osteoporosis and treatments of osteoporotic fractures in glucocorticoid tablet users in the U.S. are calculated. These costs will be defined and methods of calculations will be described in Section 3.2.5. Briefly, costs of evaluation of osteoporosis exclude costs of pharmacotherapy, and costs of fracture treatment include pharmacotherapy and surgery. It is assumed that these costs will be the same for all glucocorticoid users in the U.S. (Section 3.2.5) so only descriptive statistics will be presented. No hypothesis is needed for the third objective.

2.9.4 Hypotheses for Objective Four

Average direct medical costs of preventive anti-osteoporotic treatments (CTX) for glucocorticoid tablet users in the U.S. are calculated and compared. Subjects using preventive anti-osteoporotic treatments are those who did not have prior osteoporotic fractures. These costs are categorized by gender and type of glucocorticoid use. For the fourth study objective, the hypotheses are:

Ho_{4A1}: $CTX_{LTGS\text{-}F(BP)} = CTX_{LTGS\text{-}F(CN)} = CTX_{LTGS\text{-}F(HB)} = CTX_{LTGS\text{-}F(HT)} = CTX_{LTGS\text{-}F(RF)} = CTX_{CTL\text{-}F}$

There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for female long-term glucocorticoid users (LTGS).

Ho_{4A2}: $CTX_{LTGS\text{-}M(BP)} = CTX_{LTGS\text{-}M(CN)} = CTX_{CTL\text{-}M}$

There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for male long-term glucocorticoid users (LTGS).

Ho_{4B1}: $CTX_{HRGS\text{-}F(BP)} = CTX_{HRGS\text{-}F(CN)} = CTX_{HRGS\text{-}F(HB)} = CTX_{HRGS\text{-}F(HT)} = CTX_{HRGS\text{-}F(RF)} = CTX_{CTL\text{-}F}$

There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for female high-risk glucocorticoid users (HRGS).

Ho_{4B2}: $CTX_{HRGS\text{-}M(BP)} = CTX_{HRGS\text{-}M(CN)} = CTX_{CTL\text{-}M}$

There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for male high-risk glucocorticoid users (HRGS).

2.9.5 Hypotheses for Objective Five

Model-estimated average total direct medical costs and average effectiveness (fracture avoided) of 10-year or lifetime anti-osteoporotic treatments for glucocorticoid tablet users in the U.S. are compared. For the fifth study objective, the hypotheses are:

- Average costs of anti-osteoporotic treatments (COST)

Ho_{5A1}: $COST_{10YR\text{-}F(BP)} = COST_{10YR\text{-}F(CN)} = COST_{10YR\text{-}F(HB)} = COST_{10YR\text{-}F(HT)} = COST_{10YR\text{-}F(RF)} = COST_{10YR\text{-}F\ (CT)}$

There is no significant difference in average direct medical costs of 10-year anti-osteoporotic treatments for female glucocorticoid tablet users.

Ho_{5A2}: $COST_{10YR\ -M(BP)} = COST_{10YR\ -M(CN)} = COST_{10YR\ -M(CT)}$

There is no significant difference in average direct medical costs of 10-year anti-osteoporotic treatments for male glucocorticoid tablet users.

Ho_{5B1}: $COST_{LIFE\text{-}F(BP)} = COST_{LIFE\text{-}F(CN)} = COST_{LIFE\text{-}F(HB)} = COST_{LIFE\text{-}F(HT)} = COST_{LIFE\text{-}F(RF)} = COST_{LIFE\text{-}F\ (CT)}$

There is no significant difference in average direct medical costs of lifetime anti-osteoporotic treatments for female glucocorticoid tablet users.

Ho_{5B2}: $COST_{LIFE\ -M(BP)} = COST_{LIFE\ -M(CN)} = COST_{LIFE\ -M(CT)}$

There is no significant difference in average direct medical costs of lifetime anti-osteoporotic treatments for male glucocorticoid tablet users.

- Average effectiveness of anti-osteoporotic treatments (EFF)

Ho_{5C1}: $EFF_{10YR\text{-}F(BP)} = EFF_{10YR\text{-}F(CN)} = EFF_{10YR\text{-}F(HB)} = EFF_{10YR\text{-}F(HT)} = EFF_{10YR\text{-}F(RF)} = EFF_{10YR\text{-}F\ (CT)}$

There is no significant difference in average effectiveness of 10-year anti-osteoporotic treatments for female glucocorticoid tablet users.

Ho_{5C2}: $EFF_{10YR\ -M(BP)} = EFF_{10YR\ -M(CN)} = EFF_{10YR\ -M(CT)}$

There is no significant difference in average effectiveness of 10-year anti-osteoporotic treatments for male glucocorticoid tablet users.

Ho_{5D1}: $EFF_{LIFE\text{-}F(BP)} = EFF_{LIFE\text{-}F(CN)} = EFF_{LIFE\text{-}F(HB)} = EFF_{LIFE\text{-}F(HT)} = EFF_{LIFE\text{-}F(RF)} = EFF_{LIFE\text{-}F\ (CT)}$

There is no significant difference in average effectiveness of lifetime anti-osteoporotic treatments for female glucocorticoid tablet users.

Ho_{5D2}: $EFF_{LIFE\ -M(BP)} = EFF_{LIFE\ -M(CN)} = EFF_{LIFE\ -M(CT)}$

There is no significant difference in average effectiveness of lifetime anti-osteoporotic treatments for male glucocorticoid tablet users.

2.9.6 Hypotheses for Objective Six

Because of budget constrains, payers often establish a threshold cost-effectiveness value called the ceiling cost ratio (R_c). The R_c for this study implies the maximum willingness-to-pay (WTP) to avoid an additional incidence of osteoporotic fractures. Compared to no treatment, Buckley *et al.* reported a range of $838 to $121,125 and Homik *et al.* reported a range of $2,000 to $9,000 as the incremental costs per vertebral fracture avoided for bisphosphonates.[221, 222] Therefore, three arbitrary values of R_c are assumed for the purpose of testing hypotheses: $1,000, $10,000 and $100,000 per fracture avoided. Long-term costs and effectiveness (fracture avoided) are compared between an anti-osteoporotic treatment and the control group. Compared to the control group, the difference in model-estimated cost divided by the difference in model-estimated effectiveness for an anti-osteoporotic treatment is called the incremental cost-effectiveness ratio (ICER). For the sixth study objective, the hypotheses are:

Ho_{6A1}: $ICER_{10YR\text{-}F(BP)} = ICER_{10YR\text{-}F(CN)} = ICER_{10YR\text{-}F(HB)} = ICER_{10YR\text{-}F(HT)} = ICER_{10YR\text{-}F(RF)} \leqq R_c$

The incremental cost-effectiveness ratios (ICERs) of a 10-year anti-osteoporotic treatment for female glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, are less than or equal to the ceiling cost (R_c).

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221 Buckley, L. M. *et al*. (2003). A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *Journal of Rheumatology* 2003 30(1): 132-138.

222 Homik, J. E. *et al*. (1998). Cost-effectiveness of bisphosphonates in the prevention of corticosteroid-induced osteoporosis. *Arthritis and Rheumatism* 4(Suppl. 9): S303.

Ho_{6A2}: $ICER_{10YR\text{-}M(BP)} = ICER_{10YR\text{-}M(CN)} \leqq R_c$

The incremental cost-effectiveness ratios (ICERs) of a 10-year anti-osteoporotic treatment for male glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, are less than or equal to the ceiling cost (R_c).

Ho_{6B1}: $ICER_{LIFE\text{-}F(BP)} = ICER_{LIFE\text{-}F(CN)} = ICER_{LIFE\text{-}F(HB)} = ICER_{LIFE\text{-}F(HT)}$
$= ICER_{LIFE\text{-}F(RF)} \leqq R_c$

The incremental cost-effectiveness ratios (ICERs) of a lifetime anti-osteoporotic treatment for female glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, are less than or equal to the ceiling cost (R_c).

Ho_{6B2}: $ICER_{LIFE\text{-}M(BP)} = ICER_{LIFE\text{-}M(CN)} \leqq R_c$

The incremental cost-effectiveness ratios (ICERs) of a lifetime anti-osteoporotic treatment for male glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, are less than or equal to the ceiling cost (R_c).

2.10 SUMMARY OF CHAPTER TWO

Literature reviews indicate that bisphosphonates, calcitonin, teriparatide and vitamin D_3 have shown evidence of increasing bone mineral density (BMD) in glucocorticoid users in randomized controlled clinical trials (RCTs), and that only bisphosphonates have demonstrated preventive effects of reduction of osteoporotic fracture risks. Nevertheless, bisphosphonates may not always be the best option for every patient because an RCT usually shows the "ideal" results (efficacy) and does not reflect the "real-world" conditions (effectiveness). Other anti-osteoporotic agents may also reduce risk of osteoporotic fractures in long-term glucocorticoid users. In addition, costs related to glucocorticoid-induced osteoporosis, osteoporotic fractures and anti-osteoporotic treatments in long-term glucocorticoid users were not previously reported in the literature. More information is needed for proper management of glucocorticoid-induced osteoporosis and fractures.

Limited information was found in the literature about long-term cost-effectiveness of anti-osteoporotic treatments. Previous studies used Markov models to estimate these long-term outcomes, and the model inputs of these studies were derived from efficacy data. However, these study results may not reflect treatment realities. A study using "real-world" data as model inputs is needed.

Based on gaps in the literature and research questions identified in this chapter, six study objectives were established. Accordingly, study hypotheses were proposed and described in this chapter. The next chapter discusses the methodology for this study.

CHAPTER THREE-METHODOLOGY

This chapter describes the study methodology with brief reviews of the theoretical framework for cost-effectiveness analyses and Markov modeling. There are six sections in this chapter. The first section discusses the selection of study datasets, and describes the characteristics and structures of the study datasets. The second section defines the target population, inclusion and exclusion criteria, clinical outcomes and economic outcomes for study subjects.

The third section describes a cross-sectional analysis of the study groups. The descriptive analyses not only provide background information about study samples, but also estimate annual prevalence and incidence rates of glucocorticoid-induced osteoporosis and osteoporotic fractures and average direct medical costs associated with evaluation of osteoporosis, treatment of osteoporotic fractures and anti-osteoporosis treatments. The results of the descriptive analyses will address the first four study objectives, and these empirical statistics were used as inputs in the Markov model for this study.

The fourth section describes the theoretical framework for economic evaluations, which is the foundation of cost-effectiveness analyses. Some basic concepts and terms used in this study will be covered. The fifth section reviews the technique of modeling in economic evaluation, and describes specifications of the Markov model for this study. The longitudinal projections by using Markov modeling will address the fifth study objective. The long-term estimates of costs and fracture rates are also used in the cost-effectiveness analyses.

The sixth section highlights cost-effectiveness analyses (CEA) for this study by comparing costs and effectiveness simultaneously across anti-osteoporotic treatment options. Compared to the cost and effectiveness in the control group, the incremental cost-effectiveness ratio (ICER) of each anti-osteoporotic treatment will be calculated and reported. The results of cost-effectiveness analyses address the sixth study objective. A second-order Monte Carlo simulation is the method for probabilistic sensitivity analysis, and a one-way sensitivity analysis on annual discount rates was performed; sensitivity analyses help address parameter uncertainty in this study. Plots for cost-effectiveness and acceptability curves of treatment options for male and female glucocorticoid users are provided.

3.1 STUDY DATASETS

Information presented in Chapter Two suggests the use of empirical data for analyses in glucocorticoid users for management of glucocorticoid-induced osteoporosis and osteoporotic fractures. Even though previous studies have estimated costs and effectiveness of some anti-osteoporosis treatments, the use of hypothetical cohorts and efficacy data from randomized clinical trials yields hypothetical results, which may not reflect actual use of anti-osteoporotic treatments. The uniqueness of this study is the use of "real-world," nationally representative data to generate national estimates of costs and annual prevalence and incidence rates of osteoporosis and osteoporotic fractures in glucocorticoid tablet users. Because this information is derived from "real-world" empirical data, the study results can more appropriately facilitate decisions regarding the use of anti-osteoporotic treatments than information derived from hypotheticalal data.

The appropriateness of data is one of the keys in this study, so the first part of this section discusses potential data sources and the selection of study datasets.

3.1.1 Selection of Datasets

The best dataset would be the one which is designed and collected specifically for this study, such as primary data from a new large-scale, longitudinal follow-up observational study. However, because of budget and time constrains, the use of secondary data is more feasible for this study. Some possible, available secondary dataset candidates include Medicare datasets, Medicaid datasets, the Veterans Administration (VA) datasets, private claims datasets from insurers, hospitals, consultant firms or health systems, and data obtained from national surveys.

Some ideal features of secondary datasets for this study include: (1) representation of actual glucocorticoid users in the U.S.; (2) availability of needed economic and clinical outcomes; (3) availability of longitudinal information; and (4) easy and free accessibility. The goal of data selection is to find datasets which meet as many of these features as possible. The advantages and disadvantages of each type of datasets will be evaluated based on these features.

Medicare datasets include national, longitudinal data and information about economic and clinical outcomes, and they are accessible. However, the major covered lives in Medicare are the elderly aged 65 years old and over. This population may account for a significant percentage of population at risk for osteoporosis, but do not represent population at risk for glucocorticoid-induced osteoporosis.

Medicaid datasets include longitudinal data and information about economic and clinical outcomes. The Texas Medicaid datasets are easily accessible from the study

site. However, the major covered lives in Medicaid are the low-income or disabled people, who do not represent all glucocorticoid users. Additionally, Texas Medicaid data are regional which do not provide national information.

The Veterans Administration datasets also include longitudinal data and information about economic and clinical outcomes. The Texas VA datasets are accessible with authorization from the regional offices in Texas. However, the majority of covered lives in state VA datasets are men. It is generally believed that women account for the majority of population at risk for all types of osteoporosis. Further more, glucocorticoid-induced osteoporosis affects both men and women at any age who use prolonged glucocorticoid therapy so an ideal dataset should include both men and women at any age. Therefore, Medicare, Medicaid and the VA datasets do not fit most needs for this study.

Private claims datasets from insurers, hospitals, consultant firms or health systems usually contain data for men and women at all ages. However, the covered lives in private claims datasets are frequently limited to the regions where services or plans are available. Specially, claims datasets from hospitals likely include patients with more severe conditions than the general public. Most importantly, the acquisition of private claims datasets is usually costly. Therefore, private claims datasets do not fit the needs for this study.

There are many national surveys, including the Medical Expenditure Panel Survey (MEPS). MEPS is designed to generate nationally representative estimates of medical expenditures for the general public in the U.S. including men, women and children from newborns to 90 years old. The MEPS public datasets are free and easy to access. Most specifically, MEPS is designed for studies and projections of health and

economic outcomes in managed care.[223] MEPS datasets contain economic and clinical information needed for this study. One disadvantage of MEPS is the lack of laboratory data; specifically, the values of bone mineral density (BMD) would be an indicator of bone loss. Although having information on BMD for this study would be useful, osteoporotic fractures are the main outcomes for this study. A potential limitation is noted that subjects in MEPS were followed up for a period of two years, which may limit the generalizability of short-term outcomes for longitudinal projections. Overall, the features of good national representation, surveys designed for cost-effectiveness analyses and free access qualify MEPS as the data source which best fits the study needs among all available sources. Detailed features and the structure of MEPS datasets will be described below.

3.1.2 Medical Expenditure Panel Survey (MEPS)

3.1.2.1 Brief History of MEPS

The Medical Expenditure Panel Survey (MEPS) is a set of nationwide surveys conducted by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Health Statistics (NCHS), the U.S. Department of Health and Human Services (DHHS). Prior to MEPS, AHRQ had conducted two series of national surveys on costs and use of health care services in the U.S.: the National Medical Care Expenditure Survey (NMCES) since 1977 and the National Medical Expenditure Survey (NMES) since 1987. After modification of the survey design aiming to "capture the changing

223 AHRQ (2004). Overview of the Medical Expenditure Panel Survey. Rockville, MD. URL: http://www.meps.ahrq.gov/WhatIsMEPS/Overview.HTM (Accessed July 31, 2006).

dynamics of the health care delivery and insurance system,"[224] beginning in March 1996, MEPS has been collecting data and providing timely, "real-world," nationally representative estimates of health care utilization, expenditures, sources of payments and health insurance coverage over time in the United States.

3.1.2.2 Four Components

MEPS consists of four component surveys: the Household Component (HC), the Medical Provider Component (MPC), the Insurance Component (IC), and the Nursing Home Component (NHC). The target population of MEPS-HC is the U.S. civilian non-institutionalized population, and Hispanic Americans and Black Americans are over-sampled.[225] The sample design of the MEPS-HC includes stratification, clustering, multiple stages of selection and disproportionate sampling. The unit of survey sampling is a household, and data are collected at both household and personal levels. Sampled households were drawn from a nationally representative subsample of households who participated in the prior year's National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics (NCHS). For example, the households sampled in the 1996 MEPS-HC came from approximately one-fourth of the households sampled in the 1995 NHIS.[226]

The HC is the core survey which provides information on demographic characteristics, health conditions and status, health care utilization, charges and payments, access to care, satisfaction with care and health insurance coverage. The HC

224 Cohen, S. B. (2000). Sample design of the 1997 Medical Expenditure Panel Survey Household Component. *AHRQ Pub. No. 01-0001: MEPS Methodology Report* 11:1-18.
225 Cohen, S. B. (2000). Sample design of the 1997 Medical Expenditure Panel Survey Household Component. *AHRQ Pub. No. 01-0001: MEPS Methodology Report* 11:1-18.
226 *Ibid*.

employs an overlapping panel design. Each individual within the selected household participates in five interviews over a two-year period in one panel. For example, participants in Panel 1 had two interviews in 1996 and three interviews in 1997; participants in Panel 2 had three interviews in 1997 and two interviews in 1998 (see Table 3.1). Only selected core questions, such as health status, medical use, hospital admissions and purchase of medicines, were repeated. The medical care events reported by participants in the HC survey are further validated by contacting hospitals, physicians, home health agencies and pharmacies identified by participants.

The sum of subjects in all full-year consolidation files is 272,277, which consists of 22,601 (in 1996), 34,551 (in 1997), 24,072 (in 1998), 24,618 (in 1999), 25,096 (in 2000), 33,556 (in 2001), 39,165 (in 2002), 34,215 (in 2003) and 34,403 (2004) observations, respectively (Table 3.1). As mentioned earlier, a participant may have information for up to two years. The total number of participants identified in consolidated files from 1996 to 2004 is 151,864. The MEPS-HC overall response rates for public use files (PUFs) were 70.7% (in 1996), 66.8% (in 1997), 67.4% (in 1998), 66.0% (in 1999), 65.8% (in 2000), 66.3% (in 2001), 64.7% (2002), 64.5% (2003) and 63.1% (2004).[227]

The MPC samples comprise contacts of medical providers and pharmacies identified by participants. The MPC collects information on: (1) charges, payments and reasons for differences between the two; (2) diagnoses which are coded by ICD-9-CM (the International Classification of Disease, the ninth edition, Clinical Modification) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, the fourth version)

[227] MEPS (2007) MEPS-HC Response Rates by Panel . URL: http://www.meps.ahrq.gov/mepsweb/survey_comp/hc_response_rate.jsp. Page last revisesd on April 22, 2007; last accessed on July 7, 2007.

codes; (3) physician procedures which are classified by CPT-4 (Current Procedural Terminology, the fourth version) codes; (4) inpatient stays which are coded by DRG (diagnosis-related group) codes; and (5) prescribed medicines (medication names, national drug codes (NDC), strengths, quantity, dosages and dose forms, etc.). The MPC data are only used to supplement household expenditure data and to facilitate matching, but not to replace household data. Because of reasons such as lack of a participant's consent or a medical provider's cooperation, MPC data are not available for all reported events.

Table 3.1 The MEPS panel design and the numbers of subjects in each full-year consolidated file

	Rounds and number of subjects									
Year	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**subtotal**
Panel 1	**R1-R2** 22,601	**R3-R5** 20,868								43,469
Panel 2		**R1-R3** 13,683	**R4-R5** 12,935							26,618
Panel 3			**R1-R2** 11,137	**R3-R5** 10,440						21,577
Panel 4				**R1-R3** 14,178	**R4-R5** 13,963					28,141
Panel 5					**R1-R2** 11,133	**R3-R5** 10,855				21,988
Panel 6						**R1-R3** 22,701	**R4-R5** 21,959			44,660
Panel 7							**R1-R2** 17,206	**R3-R5** 16,788		33,994
Panel 8								**R1-R3** 17,427	**R4-R5** 16,956	34,383
Panel 9									**R1-R2** 17,447	17,447
subtotal	22,601	34,551	24,072	24,618	25,096	33,556	39,165	34,215	34,403	272,277
Response Rate	70.7%	66.8%	67.4%	66.0%	65.8%	66.3%	64.7%	64.5%	63.1%	

R1 =the first interview (round 1), R2 =the second interview (round 2), etc;

The sampling frames of the IC include employers or insurance companies identified by participants, a list of private insurance providers from the Bureau of the Census, and the public insurance programs. The IC provides information on health insurance plans in both public and private sectors. The NHC samples are obtained separately and serve as a supplement to the other components.[228] The NHC provides information on nursing home residents regarding demographic characteristics, residence history, health and functional status, utilization and expenditures for healthcare services and prescriptions. The HC data are integrated with related data from other components and presented as free public-access HC datasets by calendar years. For example, the 1998 HC, MPC and IC data are integrated and aggregated from Round 4 to Round 5 of Panel 2 and Round 1 to Round 2 of Panel 3, as indicated in Table 3.1.

3.1.2.3 Weighted Estimates

The MEPS datasets provide year-specific personal weights and variance estimates of variables for each MEPS subject in each year. The personal weights involve the household probability of selection for the NHIS, an adjustment for nonresponse and poststratification to related estimates from the Current Population Survey (CPS). These variables were used to form weighted statistics and correct standard errors that reflect national estimates for the U.S. civilian non-institutionalized population. To obtain overall weighted statistics from 1996 to 2004, data from each year are manipulated separately in most cases. This is because year-specific personal weights and variance estimates of variables are derived from year-specific data that were separately reported in different years.

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228 Cohen, S. B. (2000). Sample design of the 1997 Medical Expenditure Panel Survey Household Component. *AHRQ Pub. No. 01-0001: MEPS Methodology Report 11*:1-18.

For example, if a subject who was recruited in Panel 3 (January 1998-December 1999), received alendronate from September 1998 to June 1999, a unique identification number (RXRECIDX) for each prescription of this prescribed medicine is assigned. Alendronate should be reported by this subject in 1998 (Round 2 of panel 3), and in 1999 (Round 3 and Round 4 of panel 3). Data associated with these alendronate prescriptions are reported separately in each round. For alendronate prescriptions reported in 1998, for example, the weighted results for this subject should be calculated based on the personal weight and variance variables listed in 1998 PUFs; similarly, 1999 weighted estimates are based on variables listed in 1999 files. The weighted estimate in each year files accounts for the portion of total national estimate that the subject represents in each year.

Another example is that an osteoporotic fracture that occurred across two years for the same subject should be treated differently. It is because costs, events and medical utilization associated with this fracture were reported separately in each year's files. Additionally, the incidence of fracture is represented differently in different years because the personal weights are different in each year for the same person. Therefore, such a fracture accounts for one incidence in year one and another incidence in year two in calculations of weighted annual incidence rates of osteoporotic fractures.

3.1.2.4 MEPS Public Used Data Files (PUFs)

Data collected for MEPS in one calendar year were reported in that year's public use data files (PUFs). MEPS PUFs can be downloaded without any charge through the AHRQ web site (http://www.meps.ahrq.gov/) and are currently available from 1996 to 2004. The MEPS public use data files (PUFs) for each calendar year include (1) one

full-year consolidated data file; (2) one medical conditions file; (3) eight medical events files; and (4) two link files which were used to connect the above files. Each personal identity is replaced by a computer-generated identification number (DUPERSID), and sensitive codes are collapsed for privacy and confidentiality. Additionally, only the first three digits of ICD-9-CM condition codes and the first two digits of ICD-9-CM procedure codes are displayed in the public-access files. Figure 3.1 uses 1998 datasets as an example to demonstrate relationships among year-specific MEPS public use data files (PUFs) and variables used for file linkage. Some important variables in each year-specific public use data files are highlighted as follows.

(1) Each record in the full-year consolidated files contains personal information and a summary of selected person-level statistics for the whole year. This file is located on the left in Figure 3.1. This person-level file contains information including demographic characteristics, insurance coverage, health status, measures of satisfaction with care, total expenditures and utilization summaries which are associated with each person within that particular year.

(2) Each record in the medical conditions files represents a personal-level health condition. A specific condition identification number (CONDIDX) is assigned to each condition, with which a corresponding event identification number (EVNTIDX) can be linked by the year-specific condition-event link file. The file includes information on the start date of the condition, the round(s) during which the respondent saw doctors for this condition, whether a further treatment was recommended (yes/no), whether the respondent received follow-ups for the condition (yes/no), whether the condition was due to a fall, a flag associated with missed work/school days or bed days (yes/no), an ICD-9-CM condition code associated with the condition, an ICD-9-CM procedure code associated with the condition, and the numbers of visits (separated for prescriptions,

inpatient visits, outpatient visits, emergency room visits, office-based visits or home health events) associated with this condition.

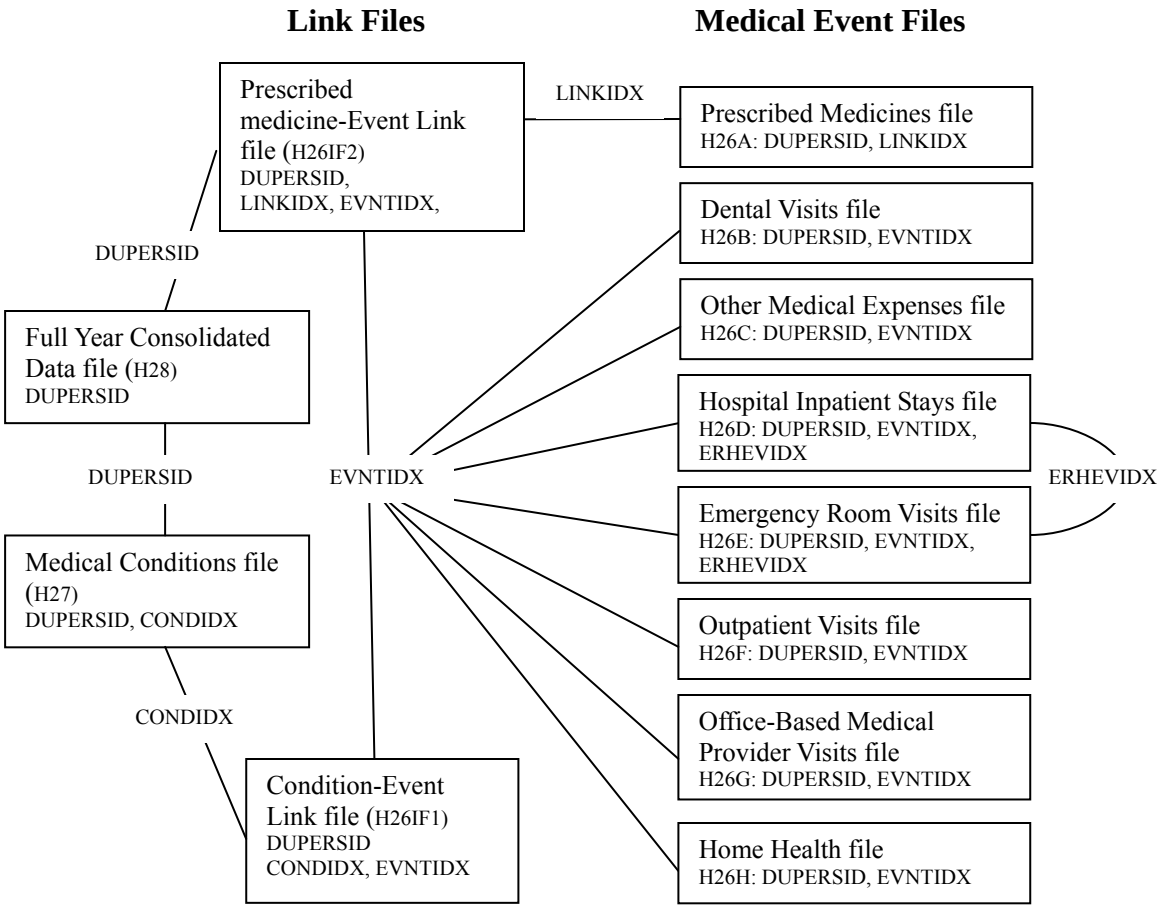

Figure 3.1 Relationships among MEPS 1998 public use data files and variables used for file linkage

(3) Each record in the medical event files represents a unique medical event, such as a prescription, an inpatient stay, etc., and information associated with that event.

There are eight types of medical events in MEPS PUFs. Selected variables in each medical event file are briefly described as follows:

(A) The **prescribed medicines** file contains a specific identification number (RXRECIDX) for each prescription, a specific identification number for linking to corresponding event (LINKIDX) and information on the date when the medicine was obtained, the round during which the medicine was reported, imputed drug name, national drug code (NDC), imputed quantity, dosage form, strength, whether obtained as a free sample (yes/no), up to three 3-digit ICD-9-CM condition codes associated with this prescribed medicine, type of pharmacy, and the amount paid (imputed/edited). The associated event can be identified via the year-specific event-link file;

(B) The **dental visits** file is not used for this study;

(C) The **other medical expenses** file contains a specific identification number for each event (EVNTIDX) and information on other medical type variables (such as glasses, insulin, medical equipment, disposable supplies, ambulance services, orthopedic items, hearing devices and bathroom aids), total number of other medical visits, flat fee variables and the amount paid;

(D) The **hospital inpatient stays** file contains a specific identification number for each event (EVNTIDX), a specific link identification number (ERHEVIDX) if the subject was admitted after an emergency visit, and information on admission date, discharge date, total number of nights for stays, the reason for admission, any operations or surgeries performed (yes/no), up to four 3-digit ICD-9-CM condition codes, up to two 2-digit ICD-9-CM procedure codes, total expenditures associated with this event, total charges, total facility charges, the actual amount paid for facility charges, total doctor fee charged and actual amount paid for total doctor fees;

(E) The **emergency room visits** file contains a specific identification number for each event (EVNTIDX), a specific ID corresponding to inpatient stays (ERHEVIDX) if the patient was admitted to a hospital after the emergency room visit, and information on the event date, any X-rays received (yes/no), any surgeries performed (yes/no), any medication prescribed (yes/no), up to three 3-digit ICD-9-CM condition codes, up to two 2-digit ICD-9-CM procedure codes, total expenditure for this event, total charges, total facility charges, the amount paid for facility charges, total doctor fee charged and the amount paid for total doctor fee;

(F) The **outpatient department visits** file contains a specific identification number for each event (EVNTIDX) and information on the event date, physician specialty, any X-rays received (yes/no), any medicine prescribed (yes/no), up to four 3-digit ICD-9-CM condition codes, up to three 2-digit ICD-9-CM procedure codes, total number of visits, total expenditure for this event, total charges, total facility charges, the amount paid for total facility charges, total doctor fee charged and the amount paid for total doctor fee;

(G) The **office-based medical provider visits** file contains a specific identification number for each event (EVNTIDX) and information on the event date, physician specialty, any X-rays received (yes/no), any medicine prescribed (yes/no), up to four 3-digit ICD-9-CM condition codes, up to three 2-digit ICD-9-CM procedure codes, total number of visits and the amount paid; and

(H) The **home health care** file contains a specific identification number for each event (EVNTIDX) and information on the event date, the event type, the type of health care worker, any home health service due to hospitalization (yes/no) or due to health condition (yes/no), any medical treatment received (yes/no), the number of days in the facility or time spent in each visit and the amount paid.

(4) Each record in two specified **link** files (IF1 and IF2) contains a set of specific identification numbers by which condition and medical events files can be linked with each other.

Study variables from each PUF are retained, files from the same year are linked and files of the same type from different years are merged. The next step is to identify study samples. In the next section, the study inclusion and exclusion criteria are described in detail.

3.2 INCLUSION AND EXCLUSION CRITERIA

This study focused on comparisons of outcomes among different anti-osteoporotic treatments in users of oral glucocorticoid steroid tablets, so each piece of information needs to be carefully defined. This section lists inclusion and exclusion criteria for study samples and definitions of anti-osteoporotic treatments, clinical and economic outcomes and comparators for analyses.

3.2.1 Target Population

The target population for this study is oral glucocorticoid tablet users in the U.S. civilian non-institutionalized population. MEPS datasets are the primary data source for this study and the target population of MEPS is the U.S. civilian non-institutionalized population, so the study population is limited accordingly. Glucocorticoid users are limited to MEPS subjects who reported use of oral glucocorticoid tablets. The definitions of study subjects are described below.

3.2.1.1 Limits to Oral Glucocorticoid Tablets

Only glucocorticoid forms which have systemic effects on bone mass loss are considered for this study. There are five reasons to include oral dosage forms and to exclude other forms of glucocorticoid steroids. First, the spray/inhaler and topical forms (such as ophthalmic drops, creams, lotions and ointments) are excluded. Next, the injections are also excluded because an injectable form is unlikely to be used by patients for long-term glucocorticoid therapy, and because many injectable glucocorticoid steroids are discontinued for safety reasons. Third, the solutions and suspensions are also excluded because topical solutions and suspensions cannot be differentiated from oral solutions and suspensions, respectively, in MEPS data. Fourth, the syrups are also excluded because this form is likely used by children who have the lowest chance to develop osteoporosis and osteoporotic fractures. Finally, the tablet form is retained because it is used for the majority of glucocorticoid users in the target population. Moreover, focusing on oral tablets makes future interpretations easier.

3.1.2.2 Study Samples

The 2001 American College of Rheumatology (ACR) Recommendation for Glucocorticoid-Induced Osteoporosis [229] and the physician's guideline from the National Osteoporosis Foundation (NOF) [230] defined long-term glucocorticoid users as users of prednisone (or its equivalent) at a minimal daily dosage of 5 mg for at least three months. However, the cumulative glucocorticoid dose is a more important indicator for bone loss

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229 ACR (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

230 NOF. (2003). Physician's guide to prevent and treatment of osteoporosis. National Osteoporosis Foundation; Washington, D.C. 1-37.

than the daily glucocorticoid dosage or the duration of glucocorticoid therapy.[231] Nonetheless, all patients on glucocorticoid therapy at any dose for any length of treatment ought to monitor possible glucocorticoid-induced bone loss, so both a broader and a restricted definition for glucocorticoid users are considered for this study: long-term glucocorticoid users (LTGS) and high-risk glucocorticoid users (HRGS). Glucocorticoid use is defined in detail in Section 3.2.2.2. It is noted that the criteria for glucocorticoid users may not cover all glucocorticoid tablets such as cases where subjects had previously received glucocorticoid therapy which was not recorded during the periods of data collection.

This study focused on subjects who have received oral glucocorticoid tablets for at least three months (long-term glucocorticoid users) and those who have received prednisone (or equivalent) tablets at a minimal cumulative dose of 450 mg (high-risk glucocorticoid users). Based on previous estimates of prevalence rates, approximately 0.7% to 0.9% of the general population received oral glucocorticoid steroids.[232, 233] Given a total unweighted number of 272,277 subjects in 1996-2004 MEPS datasets (see Table 3.1), the unweighted number of glucocorticoid tablet users in these data files is estimated to range from 1,906 to 2,450 subjects, which represents approximately 2.03 to 2.62 million glucocorticoid users in the U.S.[234]

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231 van Staa, T. P. *et al.* (2000). Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology* 39(12): 1383-1389.

232 Gudbjornsson, B. *et al.* (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

233 van Staa, T. P. *et al.* (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

234 The estimated U.S. civilian non-institutionalized population is 290,850,005 in 2003, according to the data from the U.S. Census Bureau (2005). National and state dataset in comma separated values file. The U.S.Census Bureau and Population Division, The U.S. Department of Commerce. Washington, DC.

3.2.2 Medication Use

The use of medications for this study includes the use of oral glucocorticoid tablets and the use of anti-osteoporotic agents. Each medication is described and defined. Some common definitions are listed before the definitions of medications.

3.2.2.1 General Definitions for All Medications

The MEPS prescribed medicines files include three variables (RXBEGDD, RXBEGMM and RXBEGYRX) which indicate the start date of the medication; however, some data points for these variables are missing. To estimate the start date for a prescribed medicine, the start date of the round when the prescribed medicine was reported serves as a proxy of the start date of the prescribed medicine. The variables for these reference dates include BEGRFD31, BEGRFM31, BEGRFY31, BEGRFD42, BEGRFM42, BEGRFY42, BEGRFD53, BEGRFM53 and BEGRFY53. The index date of a medication is defined as the earliest start date reported by the subject in MEPS data between 1996 and 2004. The index date for a medication is important in determining a prior experience related to osteoporosis and/or osteoporotic fractures.

The length of a treatment needs to be defined. To estimate the length of a treatment, the quantity of a medication (RXQUANTY) serves as a proxy. This definition assumes continuous use of a medication without considering compliance and possible gaps. Except for weekly use of bisphosphonates and dosage regimens for HRT, most anti-osteoporotic agents are administered once daily (i.e., the label use approved by the FDA). Therefore, the length of a treatment can be estimated by the quantity of a medication. Proper adjustments are implemented for non-once-per-day dose regimen for bisphosphonates and HRT.

The names of prescribed medicines (RXNAME) in MEPS prescribed medicines files are imputed and presented as the generic names or the most common brand names. The following names of prescribed medicines were used in this study for identifying users of glucocorticoid steroids and users of anti-osteoporotic agents. Some anti-osteoporotic agents are also used to treat conditions other than osteoporosis or fractures, so the exclusion criteria for each anti-osteoporotic agent are described.

3.2.2.2 Glucocorticoid Therapy (GS)

The use of oral glucocorticoid tablets is defined as any use of oral prednisone (or its equivalent) tablets. The glucocorticoid steroids include cortisone (cortisone acetate), betamethasone (Celestone®), dexamethasone (Decadron®, Dexameth®, Dexone® or Hexadrol®), hydrocortisone (Cortef® or Hydrocortone®), methylprednisolone (Medrol®), prednisone (Meticorten®, Orasone®, Panasol-s®, Deltasone®, Prednicen-m®, Sterapred® or Sterapred DS®), prednisolone and triamcinolone (Aristocort®). Glucocorticoid use is characterized by three indicators: cumulative glucocorticoid dose, a cumulative quantity of glucocorticoid tablets and average daily glucocorticoid dose. The strengths of different glucocorticoid steroids are converted to equivalent dosage of prednisone. Long-term glucocorticoid use (LTGS) for this study is defined as the use of oral glucocorticoid tablets for a total period of 90 days or more. High-risk glucocorticoid use (HRGS) for this study is defined as the use of prednisone (or its equivalent) at a cumulative dose of at least 450 mg (which is calculated by multiplying 5 mg of prednisone by 90 days). Table 3.2 lists the equivalent dosage of various glucocorticoid steroids to prednisone, and their corresponding 90-day accumulated dosage.

The cumulative glucocorticoid dose for each subject was calculated by summmg up the product of the glucocorticoid dose multiplied by the number of tablets for each qualified glucocorticoid prescription reported by the subject. Qualified glucocorticoid prescriptions refer to prescriptions of oral prednisone (or equivalent) tablets. The cumulative quantity of glucocorticoid tablets for each subject was calculated by summing up the the number of tablets for each qualified glucocorticoid prescription reported by the subject.

Table 3.2 Equivalent milligram and 90-day accumulated dosage of the various glucocorticoid steroids

Name	Equiv. dosage (mg)	90-day cumul. dosage (mg)	Name	Equiv. dosage (mg)	90-day cumul. dosage (mg)
Betamethasone	0.75	67.5	Methylprednisolone	4	360
Cortisone	25	2,250	Prednisolone	5	450
Dexamethasone	0.75	67.5	Prednisone	5	450
Hydrocortisone	20	1,800	Triamcinolone	4	360

Cumul.=cumulative; Equiv.=equivalent;
Reference: http://drugs-about.com/drugs/prednisolone/prednisolone-celltech.pdf

3.2.2.3 Bisphosphonates (BP)

Bisphosphonates used for this study include alendronate (alendronate sodium or Fosamax®) and risedronate (risedronate sodium or Actonel®), because the U.S. Food and Drug Administration (FDA) only approved these two products for the management of glucocorticoid-induced osteoporosis (5 mg/day or 10 mg/day for alendronate, 5 mg/day for risedronate, etc. see Table 2.1). If a dosage of 40 mg of alendronate or 30 mg of risedronate was reported, these subjects were excluded. Bisphosphonates at those doses

probably were used for Paget's disease (an ICD-9-CM code of 731). If an ICD-9-CM code of 731 was reported in any one of three variables for ICD-9-CM codes, these subjects were excluded. Adverse drug events for bisphosphonates are defined as a diagnosis of any of the following ICD-9-CM codes: 530 (disease of esophagus), 531 (gastric ulcer), 532 (duodenal ulcer), 533 (peptic ulcer, site unspecified), 535 (gastritis and duodenitis), 536 (disorders of function of stomach), 578 (Gastrointestinal hemorrhage), 787 (Symptoms involving digestive system), and 789 (Other symptoms involving abdomen and pelvis).[235, 236]

A study used a large claims database to investigate the medication costs of alendronate, risedronate and nasal calcitonin in the first year after a fracture.[237] The average annual direct medical costs for non-vertebral fractures were $320, $110 and $512 for alendronate, risedronate and calcitonin, respectively.[238] The average costs for gastrointestinal (GI) adverse reaction were $72 for alendronate and $26 for risedronate (2002 dollars).[239]

3.2.2.4 Calcium and Vitamin D Preparations (CA)

The MEPS datasets do not include information regarding over-the-counter (OTC) use of calcium and vitamin D products. The inclusion of calcium and vitamin D

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235 Miller, R. *et al.* (2004). Incidence of gastrointestinal events among bisphosphonate patients in an observational study. *The American Journal of Managed Care*, 10(7): S207-S215.

236 Kane, S. *et al.* (2004). Pharmacoeocnomic evaluation of gastrointestinal tract events during treatment with risedronate or alendronate: a retrospective cohort study. *The American Journal of Managed Care*, 10(7): S216-S226.

237 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

238 *Ibid.*

239 Kane, S. *et al.* (2004). Pharmacoeocnomic evaluation of gastrointestinal tract events during treatment with risedronate or alendronate: a retrospective cohort study. *The American Journal of Managed Care*, 10(7): S216-S226.

preparations may lead to inaccurate estimations, so calcium and vitamin D preparations are excluded as one comparison group for this study. Additionally, as mentioned in Section 2.4.1, calcium and vitamin D are frequently recommended for interventions associated with bone loss, and are frequently included in both study and control groups. It is assumed that all study subjects used calcium and vitamin D preparations daily, and that the effects of calcium and vitamin D products on fracture rates are equal. Therefore, the effects of calcium and/or vitamin D products on osteoporosis or osteoporotic fractures are not specifically considered in this study.

3.2.2.5 Calcitonin (CN)

Calcitonin is available as nasal spray (200 IU/spray) and injection (200 IU/ml). Calcitonin salmon (Miacalcin®) was approved by the FDA before 1995, so Miacalcin® users were included in this study. Calcitonin salmon recombinant (Fortical®) was approved by the FDA on Aug 12, 2005, which is beyond the study period (1996-2004), so Fortical® is not included in this study. Miacalcin® nasal spray (2200 IU/mL calcitonin-salmon in a 3.7-ml glass bottle) is usually used one spray (200 IU or 0.09 mL per spray) in one nostril each day alternating nostrils daily, so the quantity of calcitonin sprays could be the proxy for duration of therapy. A bottle of Miacalcin® provides at least 1-month supply of nasal sprays. Calcitonin can also be used for Paget's disease. If an ICD-9-CM code of 731 is reported in any of three variables for ICD-9-CM diagnosis, the subjects will be excluded. Adverse drug events for calcitonin are defined as a diagnosis of any of the following ICD-9-CM codes: 782 (symptoms involving skin and other integumentary tissue, including skin flushing) and 787 (symptoms involving digestive system, including nausea and vomiting).

3.2.2.6 Hormone Replacement Therapy (HT)

Hormone replacement therapy for this study refers to the use of estrogen-and progestin-containing drug products, including estrogen, estradiol (Alora®, Angeliq®, Climara®, Climara Pro®, Combipatch®, Esclim®, Estraderm®, Estrasorb®, Femring®, Fempatch®, Vivelle® or Vivelle-dot®), gynodiol (Estrace®), conjugated estrogen (Premarin® or Enjuvia®), esterified estrogen (Estratab® or Menest®), estropipate (Ortho-estm® or Ogen®), or estrogen and progestin combined (Activella®, femhrt®, Ortho-prefest®, Prefest®, Prempro® or Premphase®) in forms of tablets, transdermal systems (patches), emulsion/gels and vaginal rings.[240] Although the Women's Health Initiative (WHI) trial indicated that conjugated estrogens plus medroxyprogesterone increased the risks of invasive breast cancer in postmenopausal women, hormone replacement therapy is still included in this study. This is because hormone replacement therapy is believed to be frequently used during the period of 1996 and 2004 in which study data were obtained. Even if hormone replacement therapy was originally prescribed for treating postmenopausal symptoms, the effects of hormone replacement therapy on preventing osteoporotic fractures remain. However, hormone replacement therapy is not expected to be used by men for this study, so male subjects were excluded for hormone replacement therapy. Adverse drug events for hormone replacement therapy are defined as a diagnosis of any of the following ICD-9-CM codes: 174 (malignant neoplasm of female breast), 179 (malignant neoplasm of uterus, part unspecified), 182 (malignant neoplasm of body of uterus), 410-414 (ischemic heart disease), 430-438 (cerebrovascular disease), 444 (arterial embolism and thrombosis), 445

240 *Drug Facts and Comparisons* 57th ed. (2003). Wolters Kluwer Company; St. Louis, Missouri, Pages 251-266.

(atheroembolism), 451 (phlebitis and thrombophlebitis) and 453 (other venous embolism and thrombosis).[241, 242, 243, 244, 245]

3.2.2.7 Combination of Hormone Replacement and Bisphosphonate Therapy (HB)

Eleven combinations are possible: [BP-HT], [BP-raloxifene (RF)], [BP-CN], [HT-RF], [HT-CN], [RF-CN], [BP-HT-RF], [BP-HT-CN], [BP-RF-CN], [HT-RF-CN] and [BP-HT-RF-CN]. However, as mentioned in Section 2.4.7, combination therapy is currently not recommended because the small additive protective effects of using combination therapy may not outweigh increased chances of potential adverse reactions. Only the combination of hormone replacement and bisphosphonate therapy (HB) is included in this study because: (1) this combination is more popular than other combinations; and (2) this combination has demonstrated risk reduction of osteoporotic fractures compared to monotherapy of bisphosphonates or hormone replacement therapy in an observational study.[246] The observation window for the HB combination is unclear, so the inclusion criterion for length of HB therapy also depends on the inclusion

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241 Rossouw, J. E. *et al.* (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *The Journal of the American Medical Association*, 288(3): 321-333.

242 Pentti, K. *et al.* (2006). Hormone replacement therapy and mortality in 52-to 70-year-old women: the Kuopio Osteoporosis Risk Factor and Prevention Study. *European Journal of Endocrinology*, 154(1): 101-107.

243 Daly, E. *et al.* (1996). Hormone replacement therapy in a risk-benefit perspective. *Maturitas*, 23(2): 247-259.

244 Armstrong, K. *et al.* (2001). Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk. *Obstetrics & Gynecology*, 98(6): 996-1003.

245 Yu, Y. F. *et al.* (2004). Cost-effectiveness analysis of long-term hormone replacement therapy (estrogen plus progestin) in healthy postmenopausal women for osteoporosis prevention. *Value in Health*, 7(3): 296-296.

246 Tiller, W. (2004). Alendronate and hormone replacement therapy in the prevention of osteoporotic fracture: A pharmacoeconomic analysis employing a net-benefit regression method of cost-effectiveness. *Dissertation.* The University of Texas at Austin, Austin, TX. 325 Pages.

criteria for bisphosphonates in order to facilitate comparisons. Adverse drug events for this combination therapy include all ICD-9-CM codes identified as adverse drug reactions for bisphosphonates and hormone replacement therapy described previously.

3.2.2.8 Raloxifene (RF)

Raloxifene (raloxifene hydrochloride, RF) is the only FDA-approved prescribed medicine among selective estrogen receptor modulators (SERMs) for treatment of post-menopausal osteoporosis. No indication of raloxifene is for men, so male subjects are excluded. The brand name of raloxifene is Evista® which is available as 60 mg tablets. Adverse drug events for raloxifene include the same set of ICD-9-CM codes as adverse drug reactions for hormone replacement therapy.

3.2.2.9 Teriparatide (PT)

The parathyroid hormone for treating osteoporosis is teriparatide (Forteo® or PTH). The BMD reduction and the anti-fracture effect of teriparatide may be observed after one year of teriparatide therapy.[247, 248] Because Forteo® was approved in November 2002, and the publicly available MEPS datasets contain data up to 2004, the anti-fracture effects of teriparatide are likely not reported in the 1996-2004 MEPS datasets. Therefore, teriparatide is excluded in this study.

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247 Lane, N. E. *et al.* (2000). Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. *Journal of Bone and Mineral Research* 15(5): 944-951.

248 Lane, N. E. *et al.* (2000). Short-term increases in bone turnover markers predict parathyroid hormone-induced spinal bone mineral density gains in postmenopausal women with glucocorticoid-induced osteoporosis. *Osteoporosis International* 11(5): 434-442.

3.2.3 Subgroups for Comparisons

MEPS subjects are classified into subgroups by some confounding factors in order to partially control the contributions of these factors to the outcomes of interests. Important confounding factors include gender, glucocorticoid use, length of anti-osteoporotic treatments, age and the underlying conditions. However, not all of these factors are controlled in the analyses. In order to generate nationally representative estimates from MEPS data, it generally requires at least 15 subjects with positive personal weights in each subgroup.[249] If the subgroup classification does not yield a sufficient number of subjects in each subgroup, information from different levels of a factor may be used. Figure 3.2 shows a conceptual diagram of relations associated with gender, glucocorticoid use and use of anti-osteoporotic agents to overall osteoporosis and osteoporotic fractures.

It is known that men and women have different risks of osteoporosis or osteoporotic fractures, so male and female subjects should be considered separately. Subjects are also categorized into three types of glucocorticoid use: (1) high-risk glucocorticoid use (HRGS); (2) long-term glucocorticoid use (LTGS); and (3) all MEPS subjects regardless of glucocorticoid use. It is noted that these categories of glucocorticoid use are not mutually exclusive: HRGS users are usually included in LTGS users, which are included in all MEPS subjects. Among either HRGS, LTGS or MEPS subjects, there are six groups of anti-osteoporotic treatments, of which three of them were used for females only. Therefore, a total of three subgroups for men and six subgroups for women exist for each type of glucocorticoid use.

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[249] Personal communications with experienced members of the AHRQ's question & discussion group regarding MEPS.

A minimal period of 90 days for anti-osteoporotic treatments was used for all subjects who reported anti-osteoporotic medications. Two reasons support this restriction: (1) it reflects the shortest time for observing a possible incidence of osteoporotic fractures after the use of anti-osteoporotic medications; and (2) it matches a minimal period of 90 days for glucocorticoid therapy. The minimal period of observation needed to determine the anti-fracture effects of each anti-osteoporotic agent is not certain. Reports indicate that the shortest period of effective bisphosphonate therapy for preventing osteoporotic fractures is three months and for raloxifene is 12 months. A significant reduction (P =0.044) for multiple symptomatic vertebral fractures could be found as early as three months after alendronate therapy.[250] The Multiple Outcomes of Raloxifene Evaluation (MORE) study indicates that the anti-fracture effect of raloxifene could be found as early as one year after the therapy is initiated.[251, 252] There is no report in the literature about the observation period needed for other anti-osteoporotic treatments to be effective in preventing osteoporotic fractures.

The categories regarding anti-osteoporotic treatments are explained in detail below:

(1) **control (CT)** group includes subjects who may or may not report calcium/vitamin D preparations but did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

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250 Levis, S. *et al.* (2002). Alendronate reduces the risk of multiple symptomatic fractures: results from the Fracture Intervention Trial. *Journal of the American Geriatrics Society* 50(3): 409-415.

251 Ettinger, B. *et al.* (1999). Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *Journal of the American Medical Association* 282(7): 637-645.

252 Seeman, E. *et al.* (2006). Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporosis International* 17(2): 313-316.

(2) **bisphosphonate group (BP)** includes subjects who reported bisphosphonates (i.e., Actonel®, alendronate, Fosamax® or risedronate) with or without reporting calcium/vitamin D preparations but who did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

(3) **calcitonin group (CN)** includes subjects who reported calcitonin (or Miacalcin®) with or without reporting calcium/vitamin D preparations but who did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

(4) **hormone replacement therapy group (HT)** includes female subjects who reported medications listed previously for hormone replacement therapy with or without reporting calcium/vitamin D preparations but who did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

(5) The group of **hormone replacement and bisphosphonate combination therapy (HB)** includes female subjects who reported the use of both bisphosphonates and medications for hormone replacement therapy, but who did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

(6) **raloxifene group (RF)** includes female subjects who reported raloxifene (or Evista®) with or without reporting calcium/vitamin D preparations but who did not report any use of other anti-osteoporotic medications in MEPS data between 1996 and 2004;

Subjects with different ages have different risks of osteoporosis and osteoporotic fractures; the effects due to senile osteoporosis (Type 2) should be separated from glucocorticoid-induced osteoporosis. The incidence rates of osteoporosis and osteoporotic fractures are calculated separately for the following four age groups: (1) subjects aged 11 to 30 years old; (2) subjects aged 31 to 50 years old; (3) subjects aged

51 to 70 years old; and (4) subjects aged 71 to 90 years old. Therefore, effects of age should be partially controlled.

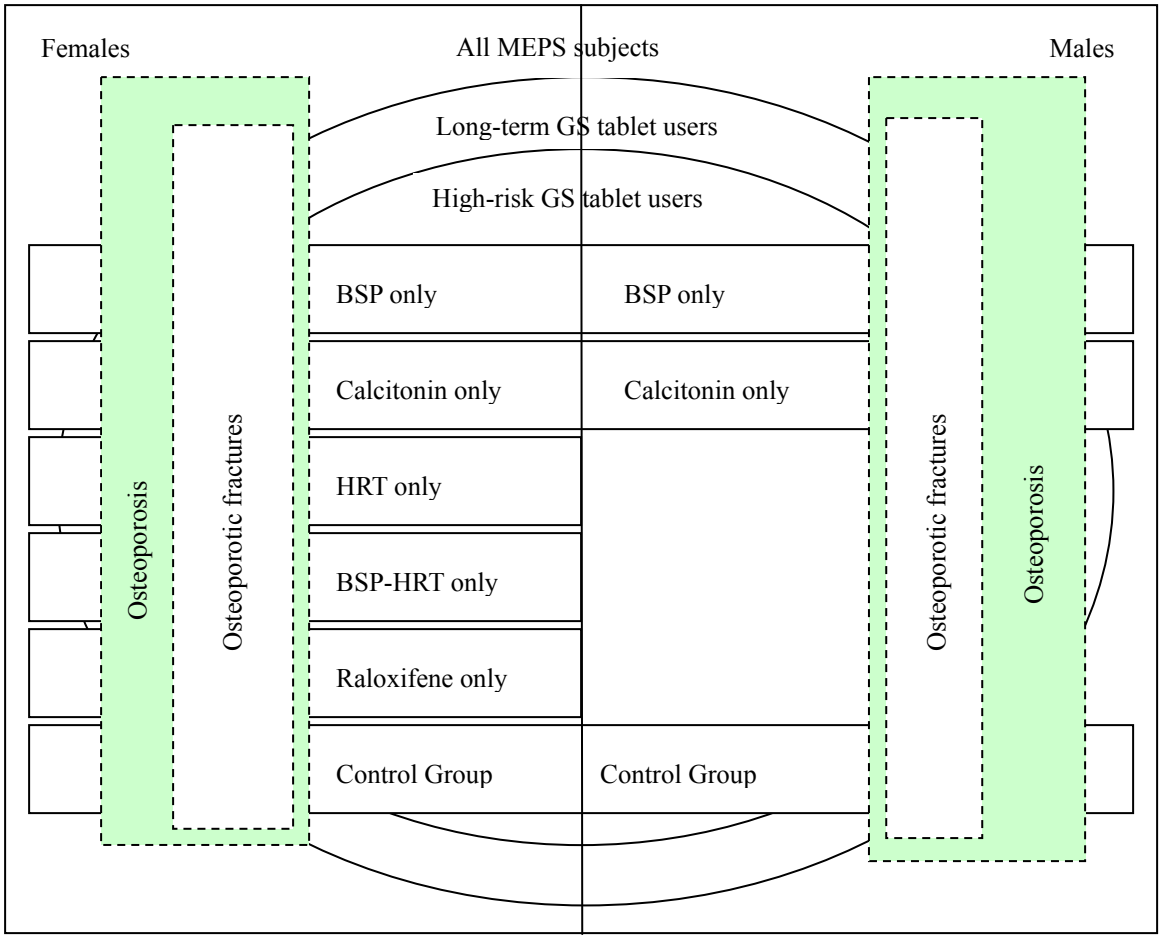

Figure 3.2 Conceptual diagram of relations associated with gender, glucocorticoid use and use of anti-osteoporotic agents to osteoporosis and osteoporotic fractures

However, the confounding effects of underlying conditions are not measurable, nor controllable in this study. However, the expected impacts of underlying conditions should be relatively lower than those from the key factors that described earlier. Moreover, if subjects were categorized in groups based on some major underlying

conditions, as mentioned in Section 2.2.2, the sample size of each subgroup would be too small to have enough statistical power for analyses.

3.2.4 Clinical Outcomes

The major clinical outcomes for this study are prevalence and incidence of glucocorticoid-induced osteoporosis and glucocorticoid-induced osteoporotic fractures. The clinical outcomes for this study are carefully defined in considerations of four factors regarding MEPS. A few assumptions are also made accordingly.

First, as mentioned in Section 3.1.2, MEPS public use files provide 3-digit ICD-9 codes. The use of 3-digit ICD-9 codes is not sufficient to precisely identify glucocorticoid-induced osteoporosis and glucocorticoid-induced osteoporotic fractures. Nevertheless, glucocorticoid-induced osteoporosis for this study is defined as the use of glucocorticoid steroids and the diagnosis of osteoporosis (Clinical Classification Code [CCC] =206 or ICD-9-CM code =733). Glucocorticoid-induced fractures are defined for this study as the use of glucocorticoid steroids and a diagnosis of: (1) pathological fractures (CCC =207); (2) vertebral fracture without spinal cord injury (ICD-9-CM code =805); (3) fracture of rib(s), sternum, larynx and trachea (ICD-9-CM code =807); (4) fracture of pelvis (ICD-9-CM code =808); (5) fracture of clavicle (ICD-9-CM code =810); (6) fracture of humerus (ICD-9-CM code =812); (7) fracture of radius and ulna (ICD-9-CM code =813); (8) fracture of neck of femur (ICD-9-CM code =820) or fracture of other unspecified parts of femur (ICD-9-CM code =821); and (9) fracture of tiba and fibula (ICD-9-CM code =823). Both close-and open-type fractures will be included because these two types can only be differentiated by the fourth digit of ICD-9-CM codes, which is not available in the MEPS public use data files (PUFs). Therefore, it is

likely that the rates of osteoporotic fractures will be over-estimated in this study. On the other side, the definitions of osteoporotic fractures for this study are relatively conservative in a comparison to a range of diagnoses for osteoporotic fractures in some studies.[253, 254, 255, 256, 257]

Second, MEPS does not capture information about the causal relationship between the use of medications and the incidence of osteoporosis and osteoporotic fractures. A few assumptions of causal relations are made for this study in order to reasonably define a new incidence of glucocorticoid-induced osteoporosis and osteoporotic fractures in MEPS. Specifically, it is assumed that when an incidence of osteoporosis or fracture occurred after use of glucocorticoid steroids, it is a "glucocorticoid-induced" event. All study subjects are glucocorticoid users, and glucocorticoid use is an important factor associated with the development of osteoporosis and osteoporotic fractures. Even if osteoporosis (or fractures) occurred before the use of glucocorticoid steroids and were caused by another factor, there is an increased risk that the glucocorticoid users with prior osteoporosis (or fractures) will remain osteoporotic (or develop another fracture). It is also assumed that when an incidence of fractures occurred after an anti-osteoporotic treatment, it is considered as "osteoporotic." The

253 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

254 Lesile, W. D. *et al.* (1997). Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. *The Journal of Clinical Endocrinology and Metabolism*, 92(1): 77-81.

255 Steinbuch, M. *et al.* (2004). Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporosis International*, 15(4): 323-328.

256 van den Boogaard, C. H. A. *et al.* (2006). Persistent bisphosphonates use and the risk of osteoporotic fractures in clinical practice: a database analysis Study. *Current Medical Research and Opinions*, 22(9): 1757-1764.

257 Johnell, O. *et al*. (2005). The burden of hospitalised fractures in Sweden. *Osteoporosis International* 16(2): 222-228.

fracture is “osteoporotic” because the major indication of these anti-osteoporotic agents, except HRT, is osteoporosis.

Third, MEPS does not collect the beginning date of a condition unless it is on the priority list. Osteoporosis and fractures are not on the priority list. However, the index date of osteoporosis or osteoporotic fractures is a key to the determination of prior experience in osteoporosis and/or osteoporotic fractures. It is problematic to determine the exact date of an incidence of osteoporosis or osteoporotic fractures. A proxy must be used. Similar to the estimation of a missing start date of a medication, the estimation of the missing condition date of osteoporosis or osteoporotic fractures can be achieved by assigning the start date of the round when the condition was reported. Again, the variables for these reference dates are BEGRFD31, BEGRFM31, BEGRFY31, BEGRFD42, BEGRFM42, BEGRFY42, BEGRFD53, BEGRFM53 and BEGRFY53. Therefore, the index date of an incidence of osteoporosis or osteoporotic fractures is defined as the earliest start date reported by the subject in MEPS data between 1996 and 2004. One record in the MEPS medical condition files is treated as one incidence of osteoporosis or osteoporotic fractures. It is also assumed that a reported fracture is a subject’s first fracture, unless more than one fracture was reported.

Fourth, MEPS does not capture events that are beyond the period of data collection. MEPS followed subjects for two years, so the MEPS data do not contain complete information regarding the medical history associated with medication use, medical conditions and events. For example, it may take more than two years for a subject to develop osteoporosis or osteoporotic fractures after glucocorticoid use. Similarly, glucocorticoid or medication use before the period of MEPS data collection was not reported in MEPS. Previous use of these medications may contribute to osteoporosis or osteoporotic fractures which were reported in MEPS later.

Additionally, a subject may only report recent use of medications because of possible recall bias. Therefore, precise determination of glucocorticoid-induced osteoporosis and osteoporotic fractures in MEPS is not feasible.

3.2.5 Economic Outcomes

The perspective of this study focuses on the payers. Direct medical costs are the major interest and will be included in this study. Direct medical costs for medical events in MEPS include costs for medications and pharmacy services (RXXPYRX), costs for other medical expenses (OMXPYRX), costs for hospital inpatient stays (IPXPYRX), costs for emergency room visits (ERXPYRX), costs for outpatient visits (OPXPYRX), costs for office-based medical provider visits (OBXPYRX) and costs for home health (HHXPYRX). Economic outcomes for this study include total costs for evaluation of osteoporosis, costs for treatment of osteoporotic fractures, costs for anti-osteoporotic medications and total costs for anti-osteoporotic treatments. Each of these four types of costs is defined as follows.

3.2.5.1 Costs for Evaluation of Osteoporosis

Costs for evaluation of osteoporosis for each subject in this study are defined as the summation of total costs for outpatient visits and office-based medical provider visits related to osteoporosis reported by the subject. Although MEPS does not explicitly specify costs of BMD tests, costs of laboratory tests, X-ray examinations, screenings and alike were included in total costs of outpatient visits and office-based medical provider visits, as indicated in the documentation of the MEPS data files. Osteoporosis-related outpatient visits and office-based medical provider visits were

identified by linking the specific condition identification number (CONDIDX) of osteoporosis to specific event identification numbers (EVNTIDX) via condition-event link files. Costs for outpatient visits (OPXPYRX) and office-based medical provider visits (OBXPYRX) related to osteoporosis for a subject were added. Because each subject was followed for two years in MEPS, the summation was divided by eight to yield the three-month average cost for evaluation of osteoporosis for each subject.

3.2.5.2 Costs for Treatment of Osteoporotic Fractures

Costs for treatment of osteoporotic fractures for each incidence in this study are defined as the summation of total costs for prescribed medicines and all type of MEPS events (RXXPYRX to HHXPYRX) which were linked to the specific condition identification number (CONDIDX) for an incidence of osteoporotic fractures via condition-link files. New incidences of osteoporotic fractures were differentiated by the first-time eisode or repeated episode for a subject. Costs were added and then divided by the total number of fracture incidences to yield an average of total costs for treatment of osteoporotic fractures per incidence.

3.2.5.3 Costs for Anti-osteoporotic Medications

Costs for each group of anti-osteoporotic medications (i.e., BP, CN, HB, HT and RF) are defined as the summation of total costs for medications and pharmacy services (RXXPYRX) listed in MEPS prescribed medicines files. Costs for the same treatment group were added, and then divided by total number of subjects in the treatment group and then divided by eight to yield the three-month average cost for the anti-osteoporotic medications per person

3.2.5.4 Costs for Anti-Osteoporotic Treatments

Total costs for anti-osteoporotic treatments are defined as the summation of costs for anti-osteoporotic medications, costs for outpatient visits and office-based medical provider visits linked to anti-osteoporotic medications, and costs for adverse drug events linked to anti-osteoporotic medications. (1) Costs for anti-osteoporotic medications have been described in Section 3.2.5.3. (2) Osteoporosis-related outpatient visits and office-based medical provider visits were identified by linking the specific prescription identification number (LINKIDX) via prescribed medicines-event link files. Total costs were added and then divided by eight to yield the three-month average for each subject. (3) Total costs for adverse reactions of an anti-osteoporotic treatment include total costs of all events associated with adverse conditions and total costs of prescribed medications associated with adverse conditions. Possible adverse drug reactions are defined in Section 3.2.2 for each anti-osteoporotic medication. These conditions with specific identification numbers (CONDIDX) were identified by ICD-9-CM codes; however, these conditions were not necessarily associated with adverse drug reactions. These CONDIDX were linked to events to obtain specific event identification numbers (EVNTIDX) via condition-event files. Events related to adverse drug reactions for a group of anti-osteoporotic medications were identified by linking the specific prescription identification number (RXRECIDX) via prescribed medicines-event link files. By linking these EVNTIDX, associated medical events (such as emergency room visits, etc.) and prescribed medicines other than the anti-osteoporotic medication were identified. Costs for events and prescribed medicines (other than anti-osteoporotic medications) were added and divided by eight to yield the three-month average cost for a subject.

3.2.5.5 Costs That Are Excluded

Direct medical costs associated with glucocorticoid therapy, including costs for glucocorticoid steroids and treatments of the underlying conditions, are not considered because the use of anti-osteoporotic agents is the main focus in this study. Indirect costs (e.g., work loss) and direct non-medical costs (e.g., travel, hotel, meals) were excluded because related data in MEPS are neither complete nor accurate. Although MEPS provides detailed information which could differentiate costs among different sources of insurance, cost analyses of insurance sources are beyond the study scope. Costs associated with death were not included.

3.2.5.6 Examples

An example is provided to demonstrate the identification of direct medical costs in MEPS data. Figure 3.3 illustrates relations among MEPS public use files for identification of costs associated with bisphosphonates (BP) for a subject (Z) and identification of costs for osteoporotic fracture (FX). The steps are:

(A) Costs of bisphosphonates:

(1) **Identification and costs of bisphosphonates:** Qualified bisphosphonates (e.g., BP_1=alendronate prescription A, BP_2=alendronate prescription B, BP_3= alendronate prescription C) were identified based on appropriate criteria (e.g., ICD-9 codes ≠731 to exclude Paget's disease, length of therapy ≧ 90 days) from the prescribed medicine files. Each prescription (BP_1 to BP_3) had a specific linkage identification number ($LINKIDX_1$, $LINKIDX_2$ and $LINKIDX_3$, respectively) for subject Z with a personal weight (wt).

The costs for a bisphosphonate prescription were found accordingly (RXXPYRX=C_1, C_2 and C_3, respectively). Total medication cost for bisphosphonates was the summation of C_1, C_2 and C_3 for subject Z. The three-month cost for subject Z was calculated by dividing the sum by eight. The average cost for all subjects in the bisphosphonate treatment group is one of the costs identified in Section 3.2.5.3;

(2) **Identification of medical events associated with bisphosphonates**: The corresponding medical events (e.g., office-based medical provide visits and outpatient visits) with specific event identification numbers (EVNTIDX) were identified for subject Z by using the LINKIDX via a prescribed medicine-event link file;

(3) **Identification and calculation of total costs for medical events associated with bisphosphonates**: The total cost of each medical event (EVNTIDX) was found for subject Z. This step was repeated for identifying costs for office-based medical provider visits and outpatient visits (i.e., C_4 and C_7) in the related medical event file. Total costs are the summation of C_4 and C_7 for subject Z by using DUPERSID. The three-month cost for office-based medical provide visits and outpatient visits was calculated by dividing the sum by eight. The average cost for all subjects in the bisphosphonate treatment group is the second type of costs identified in Section 3.2.5.4;

(4) **Identification and calculation of total costs for adverse drug reactions associated with bisphosphonates**: Specific condition identification numbers (e.g., $CONDIDX_4$) were identified by selecting ICD-9 codes for possible adverse drug reactions related to bisphosphosnate treatments. The corresponding event identification numbers (e.g., $EVNTIDX_2$ to $EVNTIDX_5$) were identified by using CONDIDX via a condition-event link file. Only those events (e.g., $EVNTIDX_6$) linked to bisphosphonate prescriptions (linking $LINKIDX_1$, $LINKIDX_2$, etc. via prescribed medicine-event files) were adverse drug events and costs of these events were added. Next, these adverse

drug events were linked to prescriptions other than anti-osteoporotic medications via prescribed medicine-event files ($EVNTIDX_6$-LINKIDX); these prescriptions were associated with treatments of adverse drug reactions. Costs of these prescriptions were added. The summation of costs of adverse drug events and prescriptions (other than anti-osteoporotic medications) was the total cost for adverse drug reactions associated with bisphospohonate treatment for subject Z. The three-month cost for adverse drug reactions related to bisphosphonate treatments was calculated by dividing the sum by eight. The average cost for all subjects in the bisphosphonate treatment group is the third type of costs identified in Section 3.2.5.4.

(B) Costs of osteoporotic fracture (FX):

(1) **Identification of fractures (FX):** Specific condition identification numbers (e.g., $CONDIDX_3$) were identified by selecting ICD-9 codes for osteoporotic fractures;

(2) **Identification of medical events associated with fractures (FX):** The corresponding event identification numbers (e.g., $EVNTIDX_2$ to $EVNTIDX_5$) were identified by using CONDIDX via a condition-event link file. In this example, $EVNTIDX_2$ was an emergency room visit and $EVNTIDX_3$ was a hospitalization. ERHEVIDX links $EVNTIDX_2$ and $EVNTIDX_3$, so the hospital admission was based on an emergency room visit resulting from an osteoporotic fracture ($CONDIDX_2$). $EVNTIDX_4$ was an outpatient visit for follow-up after the hospitalization for the fracture. $EVNTIDX_5$ was for home health care after the hospitalization for the fracture;

(3) **Identification of costs for bisphosphonate treatments associated with fractures (FX):** Bisphosphonates associated with osteoporotic fractures were identified by linking EVNTIDX to LINKIDX via prescribed medicine-event link files. Costs of

bisphosphonates (C_1 to C_3) were obtained accordingly. Total costs for bisphosphonates associated with osteoporotic fractures were the summation of C_1, C_2 and C_3;

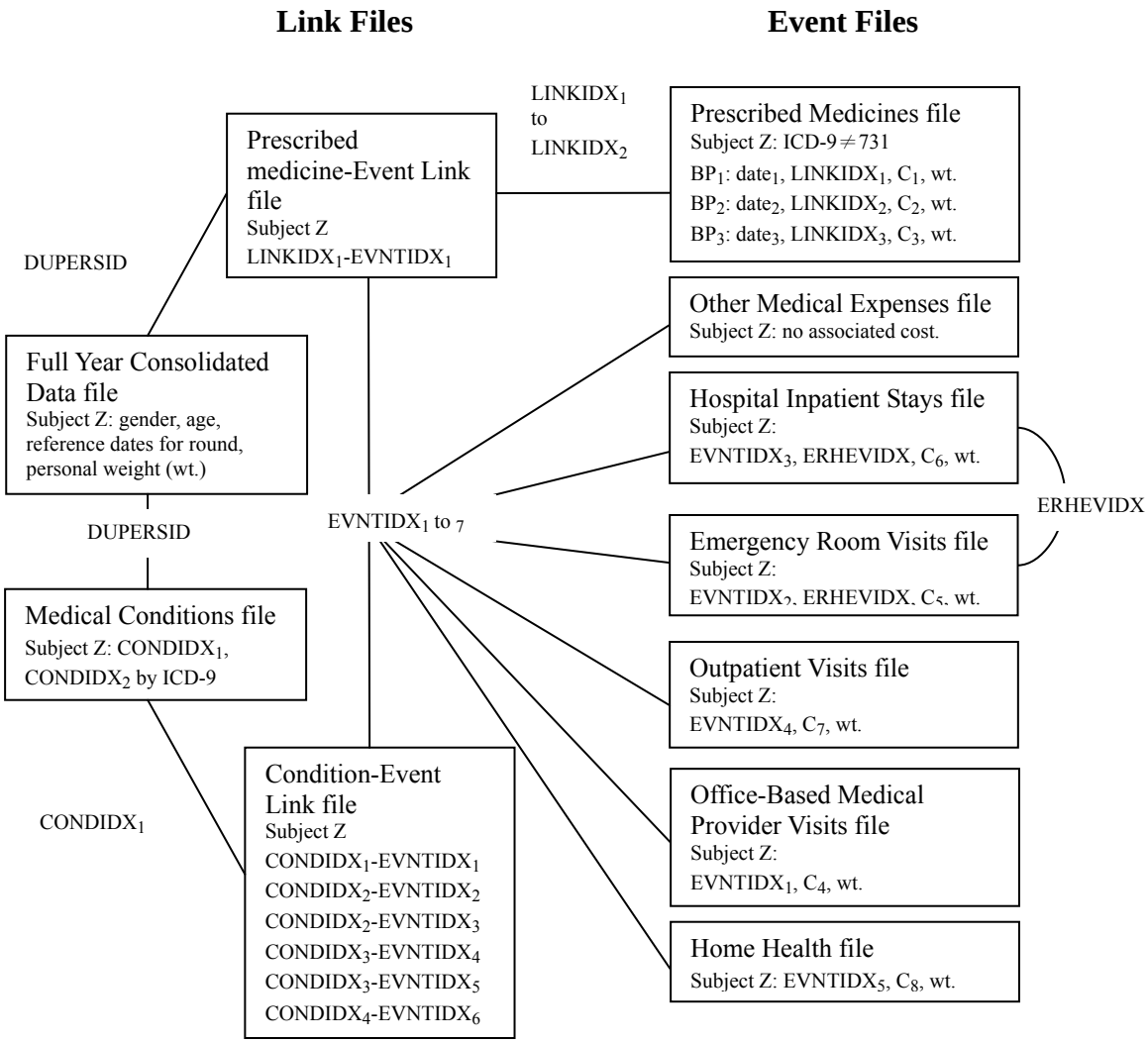

Figure 3.3 An example of identification of costs associated with an anti-osteoporotic agent (BP) and osteoporotic fracture (FX) for a subject (Z) in MEPS data

(4) **Calculation of costs associated with fractures (FX):** Total costs for treatment of osteoporotic fractures were the summation of the above total costs for medical events and bisphosphonates in this example.

3.2.5.7 Weights and Discount on Costs

Costs previously described are original values without weighting to reflect the national estimates. MEPS provides sampling weights which reflect adjustments for survey non-response and to the Current Population Survey conducted by the U.S. Bureau of the Census. Each individual has different personal weights in different years. In a traditional approach with simple random sampling (SRS), the weighted values can be calculated by simply multiplying the value by the corresponding personal weight in that specific year, as shown in the following equation. All related weighted values can be summed up or averaged to yield a weighted total or a weighted mean.

$$Y_i = W_i \times X_i$$

$$\overline{Y}_i = \frac{\sum_{i=1}^{n} W_i \times X_i}{n}$$

Where Y_i =weighted value in year *i*; W_i =personal weight in year *i*; X_i =Value in year *i*; $\overline{Y}_i$ =average weighted value.

However, MEPS employed a complex multistage sampling design, including stratification, clustering, multiple stages of selection and disproportionate sampling. The approach with simple random sampling (SRS), as described in previous paragraph could not be used to yield accurate national estimates of variance. To obtain accurate

estimates of variance from the MEPS data, standard errors associated with the weighted estimates can be derived by an appropriate technique;[258] the most commonly cited and used approach is the Taylor-series linearization method.[259] One of the statistical software packages applying the Taylor approach to estimate weight-associated standard errors is SAS (version 8.2 or higher).[260] SAS version 9.1.3 with the Service Pack 4 (SP4) updates was used for this study. SAS/STAT provides the SURVEYMEANS procedure for producing weighted means and total costs, and the SURVEYFREQ procedure for computing national estimates of weighted frequencies and percentages.

All costs are presented as 2005 dollars based on discount rates derived from the Consumer Price Index (CPI).[261] Table 3.4 lists annual U.S. CPIs based on city average costs for medical care services from 1996 to 2005, and calculated annual discount rates. The CPI for medical care services was selected based on the best estimate for matching expenditures in MEPS. For example, the discount rate of costs for yr1 is calculated as the difference in annual U.S. city average costs for medical care services between yr1 and yr2 divided by the annual U.S. city average cost for medical care in yr1. The converted value in yr2 dollars is calculated by multiplying the original value in yr1 by (one plus the discount rate for yr1). Mathematical equations are as follows.

$$\text{Discount rate}_{\text{yr1}} = \frac{CPI_{yr2} - CPI_{yr1}}{CPI_{yr1}}$$

258 AHRQ (2003). Computing Standard Errors for MEPS Estimates Agency for Healthcare Research and Quality; Rockville, MD. URL: http://www.meps.ahrq.gov/factsheets/FS_StandardErrors.htm (Accessed July 31, 2006).
259 Woodruff, R. (1971). A simple method for approximating the variance of a complicated estimate. *Journal of the American Statistical Association* 66: 411-414.
260 Intelligent property by SAS Institute Inc., Cary, NC, USA.
261 Consumer Price Index (not seasonally adjusted), Bureau o f Labor statistics, U.S. Department of Labor. Washington, DC. Available online from URL: http://data.bls.gov/cgi-bin/surveymost?cu or http://data.bls.gov/cgi-bin/surveymost/ (Accessed Aug. 14, 2006).

$$Cost_{yr2} = Cost_{yr1} * (1 + \text{discount rate}_{yr1})$$

Table 3.3 Annual U.S. Consumer Price Index (for medical care services) and calculated discount rates (1996 to 2005)

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
CPI§	232.4	239.1	246.8	255.1	266.0	278.8	292.9	306.0	321.3	336.7
Multiplier of the year to 2005†	1.448795	1.408197	1.364263	1.319875	1.265789	1.207676	1.149539	1.100327	1.04793	1
Discount rate to previous year (%)‡	2.8830	3.2204	3.3630	4.2728	4.8120	5.0574	4.4725	5.0000	4.7930	0

§ Consumer Price Index (not seasonally adjusted) based on Annual U.S. city average costs for medical care services, Bureau of Labor statistics, U.S. Department of Labor., See reference 260.
† For conversion of values to 2006 U.S. dollars;
‡ For conversion of values to U.S. dollars in previous year

3.3 CROSS-SECTIONAL ANALYSES OF MEPS DATA

The third section describes cross-sectional analyses of MEPS data. The analyses aim to obtain descriptive statistics for this study. Specifically, this analysis will yield the following descriptive statistics:

(1) Characteristics of study subjects (i.e., number of subjects in each subgroup, average age, percentages in gender and percentages in race), glucocorticoid use (i.e., average cumulative dose of glucocorticoid tablets, cumulative quantity of glucocorticoid tablets and average daily glucocorticoid dose). These characteristics are further summarized for subjects in different subgroups classified by gender, type of glucocorticoid use (i.e., MEPS, LTGS or HRGS) and type of anti-osteoporotic treatments (i.e., BP, CN, CT, HB, HT and RF). These results address the first study objective;

(2) National estimates of prevalence and incidence rates of glucocorticoid-induced osteoporosis and osteoporotic fractures in glucocorticoid users. These rates are calculated separately in subgroups classified by gender, four age groups

(i.e., four ranges of ages between 11-30, 31-50, 51-70 or 71-90), type of anti-osteoporotic treatments (i.e., BP, CN, CT, HB, HT and RF) and type of glucocorticoid use (MEPS, LTGS or HRGS). These results address the second study objective;

(3) National estimates of average direct medical costs associated with evaluation of osteoporosis and treatment of osteoporotic fractures in glucocorticoid users. The results help address the third study objective; and (4) national estimates of average direct medical costs associated with anti-osteoporotic agents and treatments in glucocorticoid users. The results address the fourth study objective. As mentioned in Section 3.2.5.7, the SURVEYMEANS procedure was used to compute averages and standard error of the means, and the SURVEYFREQ procedure was used to produce national estimates of weighted numbers and percentages. These descriptive statistics were used as model inputs to estimate long-term outcomes in the Markov modeling (which will be explained in Section 3.5.3).

Analyses of variance (ANOVAs) were used for testing study hypotheses for objectives one, three and four. The SAS SURVEYMEANS procedure was used for comparing weighted means by ANOVA models. An alpha level of 0.05 was used for the ANOVAs.

Logistic regression analyses were performed to investigate relative risks of osteoporotic fractures between long-term glucocorticoid users and non-glucocorticoid users in MEPS subjects. The SAS SURVEYLOGISTIC procedure was used. The dependent variable is incidence of osteoporotic fractures; the independent variables are age, gender (male/female), glucocorticoid use (yes/no), BP treatment (yes/no), CN treatment (yes/no), HT treatment (yes/no), HB treatment (yes/no) and RF treatment (yes/no). The results were used to estimate incidence rates of osteoporotic fractures in some subgroups with small sample sizes. Because incidence rates of osteoporotic

fractures are calculated separately in subgroups classified by different ranges of age, gender and type of anti-osteoporotic treatments, the sample size of some subgroups was too small (or zero) to generate national estimates for incidence rates of osteoporotic fractures.

3.4 THEORETICAL FRAMEWORK OF ECONOMIC EVALUATIONS

In situations involving scarce resources, decisions are often needed to allocate those resources. In the healthcare sector, this frequently refers to allocating a payer's budget for optimal medical utilization. For this study, the decision is translated to how much extra money payers should pay to avoid one episode of glucocorticoid-induced osteoporosis or fractures. Many economic evaluation approaches have been proposed in the past few decades. Cost-effectiveness analysis is probably the most frequently used technique for decision analyses. This section briefly outlines the theoretical framework of decision analysis, especially for cost-effectiveness analysis.

3.4.1 Basic Concepts in Decision Analysis

Welfare economics is used as the theoretical foundation for many economic evaluations. It is assumed that each individual pursues his or her maximal utility or benefits, and the social welfare is the summation of utilities across all individuals. However, because of limited resources and possible conflicts among individuals, allocation of resources is usually needed to reach the maximal overall social welfare. An economic model is built upon equilibrium of the competitions.[262] An example is

262 McGuire, A. (2001). Theoretical concepts in the economic evaluation of health care. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care-Merging Theory with Practice.* Oxford University Press: New York; Pages 1-21.

that a pharmaceutical manufacturer wants maximal profits by re-allocating outputs of all productions of various pharmaceutical products given a budget. Another example is that a re-allocation of a pharmacist's counseling time is needed to reach maximal benefits for patients receiving pharmaceutical interventions (e.g., education on prevention of fractures due to falls).

Paretian Welfare Economics is the conceptual basis of classic welfare analysis. The core is Pareto optimality, which includes two concepts: Pareto improvement and Pareto efficiency. Pareto improvement refers to the scenario that ALL individuals GAIN from the re-allocation of resources. Pareto efficiency occurs when AT LEAST one individual GAINS from the re-allocation and NO individual LOSES.[263] Given the pharmaceutical manufacturer as an example, optimality of pharmaceutical production occurs when a re-allocation increases outputs of a pharmaceutical product without decreasing outputs of other pharmaceutical products. Another example is that, given a contracted insurance premium, optimality of member care is achieved when the health insurance plan defines what health care services should be covered and what are not. When the decision of coverage is made, the majority of members should benefit from the plan and no member should be harmed.

In most "real-world" cases, some people gain (from an intervention) and others lose; Pareto optimality could never be reached. From the perspective of social welfare, when a public policy is considered, a better re-allocation of resources is to yield maximal benefits to most individuals but minor losses to a few individuals in comparison with the baseline. A solution is that potential gainers of one resource compensate potential losers with another resource for exchange, so ideally there is no absolute loser after all in

263 McGuire, A. (2001). Ibid.

theory.[264] An example is the negotiation of insurance premiums for covered prescriptions in formularies between health insurance companies and payers. Health insurance companies will get a rebate or discount from a pharmaceutical manufacturer for listing preferred pharmaceutical products in formularies; plan sponsors and members experiences formulary restrictions but pay lower insurance premiums. Another example is that a patient decides whether s/he should pay more money (a loss) in exchange for better patient care (a gain).

However, individuals value resources differently, so benefits enjoyed by gainers may be different than those by losers. Insurance companies and plan sponsors/members may have different values of gains and losses for formulary restrictions, for example. Different patients have different values for patient care. A practical approach is to value resources in terms of monetary values. The no-loser constraint with hypotheticalal compensation and monetary valuation in outcomes serves the theoretical foundation of cost-benefit analysis (CBA). Cost-benefit analysis is a technique to test whether the sum of the monetary values of all gainers exceeds the sum of monetary values of all losers.[265] Cost-effectiveness analysis (CEA) can be viewed as a special case of cost-benefit analysis, where utility is measured and compared as a natural unit instead of transforming it to a monetary value.

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264 Tsuchiya, A. & Williams, A. (2001). Welfare economics and economic evaluation. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care*. Oxford University Press; New York. Pages 22-45.

265 Tsuchiya, A. & Williams, A. (2001). Welfare economics and economic evaluation. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care*: Oxford University Press; New York. Pages 22-45.

3.4.2 Basic Concepts of Cost-Effectiveness Analyses

Cost-effectiveness analyses can be performed with a decision tree to aid decision making. A traditional decision tree has one decision node (shown as a square) at the root, several branches off the decision node to represent competing alternatives, a chance node (shown as a circle) with branches to represent different outcomes/events and a terminal node (shown as a triangle) at the end of each branch to represent final outcomes.

The expected value (EV) of the utility (such as costs and effectiveness) for each alternative is calculated as the probability-weighted summation of utilities in branches related to the corresponding alternative.

$$\text{Expected value (EV)} = \sum_{i=1}^{n} \text{Pi} \times \text{Ui}$$

where P*i* is the probability of selecting branch i; U*i* is the utility in branch i, branches are numbered from 1 to n.

Comparisons of both costs and effectiveness of one alternative with those of another option (that is usually the standard option) lead to a selection of the preferred alternative with a lower cost-effectiveness ratio. Any alternative with both a higher cost and lower effectiveness than the reference is dominated and can always be rejected for strategy selection. Similarly, any alternative with both a lower cost and higher effectiveness than the reference dominates. The null hypothesis of cost-effectiveness analysis is that the mean cost-effectiveness of one alternative equals that of another competitor.

$$Ho: \frac{Ca}{Ea} - \frac{Cb}{Eb} = 0$$

where Ca (Cb) is total costs of alternative a (b); Ea (Eb) is total effectiveness of alternative a (b).

However, when an alternative has both higher costs and effectiveness, or both lower costs and effectiveness than the relevant alternative, the selection is not clearly made. A solution is to calculate the incremental cost-effectiveness ratio (ICER), which means the incremental cost per additional unit of outcome. If the ICER of an alternative is less than the maximum acceptable cost-effectiveness ratio (or ceiling ratio, Rc), this alternative is preferable. Frequently, the ceiling ratio (Rc) is set arbitrarily based on budget constraints, willingness-to-pay (WTP), and similar considerations. The null hypothesis could be formulated as the incremental cost-effectiveness ratio (ICER) equals the maximum acceptable cost-effectiveness ratio (or ceiling ratio, Rc).

$$Ho': ICER = \frac{Ca - Cb}{Ea - Eb} = \frac{\Delta C}{\Delta E} = Rc$$

where Ca (Cb) is total costs of alternative a; Ea (Eb) is total effectiveness of alternative a (b); ΔE is incremental effects between alternatives a and b; and ΔC is the incremental costs between alternatives a and b.

A major problem with this approach is that ICER approaches infinity as the denominator approaches zero. A new method to overcome this problem is the net-benefit approach.[266, 267]

266 Stinnet, A. & Mullahy, J. (1998). Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Medical Decision Making* 18: S68-S80.

Net monetary benefit: $NMB = Rc\Delta\overline{E} - \Delta\overline{C}$

Net health benefit: $NHB = \Delta\overline{E} - \frac{\Delta\overline{C}}{Rc}$

where Rc is a threshold ICER in cost-effectiveness analyses; $\Delta\overline{E}$ is the average of incremental effects between alternatives and the reference; and $\Delta\overline{C}$ is the average of incremental costs between alternatives and the reference.

Other advantages of using the net benefit method include: (1) the variance for the net-benefit statistic can be calculated by using standard methods of calculations for statistics (e.g., confidence intervals, normal distributions); (2) cost-effectiveness acceptability curves can be produced; and (3) the regression-type framework allows the addition of more explanatory variables in the model to directly examine the impact of these variables on cost-effectiveness.[268] Net benefit framework is useful when confidence intervals are desired. The issue of confidence intervals for ICERs will be discussed in Section 3.5.4.

3.5 LONGITUDINAL PROJECTION

The fifth section highlights the theoretical concepts associated with techniques of modeling, and describes specifications of parameters in the Markov model for this study.

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267 Briggs, A. H. (2001). Handling uncertainty in economic evaluation and presenting the results. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care*; Oxford University Press, New York. Pages 172-214.

268 Hock, J. S. *et al.* (2002) Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econimics* 11(5): 415-430.

Many patients with chronic conditions receive glucocorticoid therapy for a long period of time. Given the empirical sources of short-term data, modeling is needed to project the long-term estimates of costs and effectiveness related to glucocorticoid-induced osteoporosis and fractures.

3.5.1 Techniques of Modeling

Collecting longitudinal data from a large population-based randomized clinical trial of prolonged glucocorticoid therapy is unlikely to be feasible in terms of time, money, effort and ethics. Available clinical data are usually limited to criteria-restricted samples, relatively small sample sizes and short-term outcomes, but economic evaluation considers outcomes over the lifetime of individuals. Likewise, observational data are subject to many confounding issues, and tend to provide information only on surrogate endpoints, so a synthesis of existing evidence is necessary. Mathematical techniques are often required to synthesize data from different sources and extrapolate from available, short-term data to long-term or lifetime estimates for decision analyses.

Deterministic and probabilistic models are two common types of mathematical decision models. A model is called deterministic when parameters and variables are well defined and do not randomly vary; in this case, the system always generates the same results and same prediction over time when all subjects start with the same initial conditions. When the values of parameters and variables depend on chance, the model is probabilistic. In "real-world" health models, neither pure deterministic nor probabilistic models exist. The selection of model types mainly depends on the nature of disease, model structure, assumptions which simplify the model and information requested.

Stochastic processes, a class of probabilistic models, are the most common approach in time-dependent health decision analyses. Stochastic processes are popular because they can be applied to time-series analyses. Basically, a stochastic process is a sequence of variables governed by probability. Time could be divided into sequential pieces (treated as either discrete or continuous) and (probabilistic) variables within each piece could be analyzed separately. In statistics, a stochastic process is also known as a time series.

Markov models are frequently used in health economic evaluation. A Markov process is one class of stochastic processes and could be discrete or continuous with respect to time and/or states. For example, in a discrete-time Markov chain, all parameters and variables are fixed in each state during one cycle, and (probabilistic) changes occur only at the end of each cycle. Next, the technique of Markov modeling is briefly outlined, followed by the simulations and handling of uncertainty.

3.5.2 Basic Concepts of Markov Modeling

Markov decision models have a relative advantage over traditional decision analyses. Traditional decision analyses sometimes require a bulky structure of trees (possibly with endless branches) in order to fully describe a disease with repeated events over time, such as cancer recurrence and osteoporotic fractures. Furthermore, the simple decision tree cannot specify the point of time when the event occurs. A Markov decision model can be a time-dependent model, and is ideal for modeling the natural progress of a disease and the recurring events. Unlike other stochastic processes, Markov models are characterized by six components: structure, cycle, initial and

transition probabilities, Markov property, termination condition and rewards. Each of these components is discussed below.

3.5.2.1 Model Structure and Markov Cycle

A Markov model contains mutually exclusive and collectively exhaustive states, which are referred to as Markov states. In health-related models, the states should reflect the disease progression including recurring event(s). Each subject must be assigned to only one health state at any one time. The length of residence is the Markov cycle, which depends on the nature of the disease. A disease with quick progression or fast recurrences needs a short Markov cycle to represent the nature of the condition. A temporary state could represent a short-term effect of an event, in which subjects stay for only one cycle and must leave at the end of the cycle. A tunnel state is a series of temporary states and it restricts all subjects to follow a fixed path. Temporary or tunnel states are useful to describe special events, such as an adverse drug event and its treatments which do not have any impact on other states.

3.5.2.2 Initial and Transition Probabilities

At the very beginning of the Markov cycle, subjects are distributed to states based on initial probabilities. At the end of each Markov cycle, each subject is allowed to either stay in the same state (except for temporary states), or move to another state (except for the absorbing state, such as death, where no subject can exit). The net probabilities of re-distributing subjects from one state to another during a cycle are called

transition probabilities.[269, 270, 271] It is noted that transition probabilities for a specific state can be temporarily adjusted by adding a temporary or tunnel state.[272]

In the literature, rates are frequently reported instead of probabilities; each represents a different meaning. The rate is instantaneous and expresses the occurrence of an event per unit time. It can be directly converted to different time intervals; for example, the monthly rate equals to the annual rate divided by 12. The probability is the overall likelihood that an event will occur. Unlike a rate, a probability must range from zero to one, and the conversion between time intervals is not intuitive.

Given a constant or average rate (r) during a specified time (t), the probability (P) can be calculated by the following equation:[273, 274]

$$P = 1 - e^{-rt}$$

3.5.2.3 Markov Property and Termination Condition

Generally, transition probabilities in a Markov process may vary over time. This variability is commonly found in health models; for example, mortality rates increase with an increased age. If transition probabilities remain constant over time, it is called a Markov chain, which is a special case of Markov processes. Markov models treat

269 Beck, J. R. & Pauker, S. G. (1983). The Markov process in medical prognosis. *Medical Decision Making* 3(4): 419-458.
270 Sonnenberg, F. A. & Beck, J. R. (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making* 13(4): 322-338.
271 Briggs, A. H. & Sculpher, M. J. (1998). An introduction to Markov modeling for economic evaluation. *Pharmacoeconomics* 13(4): 397-409.
272 Hunink, M. G. M. *et al.* (2001). Recurring events. In: Hunink, M. G. M.; Glasziou, P. P. (editors) *Decision Making in Health and Medicine.* The Press Syndicate of the University of Cambridge; Cambridge, Pages 305-338.
273 Beck, J. R.; Pauker, S. G. (1983). The Markov process in medical prognosis. *Medical Decision Making* 3(4): 419-458.
274 Sonnenberg, F. A. & Beck, J. R. (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making* 13(4): 322-338.

everyone in the same state as equal (i.e., they have the same expected values of outcomes, same transition probabilities, etc.) during that state residence. In other words, all subjects in the same state during any cycle have equal probabilities and utilities without considering individual past experiences. Therefore, Markov processes have no memory for previous cycles, so transition probabilities depend only on the current state, not on past states. This is referred as the Markovian assumption or Markov property. In order to model disease progression with a reasonable, finite number of health states, the Markovian assumption and a termination condition are needed. In time-dependent models, the Markov process is terminated when an arbitrary number of cycles is reached or all subjects enter an absorbing state (such as death).

3.5.2.4 Rewards

The calculation of Markov rewards is very similar to the calculation of expected values, as expressed by the equation:[275]

$$\text{Rewards} = \sum_{i=1}^{n} \text{Ti} * \text{Ui}$$

where T*i* is the average cycle time in state i; U*i* is the utility in state I; and states are numbered from 1 to n.

The rewards can be obtained in three ways: (1) matrix algebraic solutions; (2) the Markov cohort simulation; and (3) the first-order Monte Carlo simulation. In a model

275 Sonnenberg, F. A. & Beck, J. R. (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making* 13(4): 322-338.

with time-independent Markov chains, all transition probabilities are fixed so the expected length of time for an individual can be calculated by using simple matrix algebra. In a model with a time-dependent Markov process, the Markov cohort simulation is a deterministic approach and the first-order Monte-Carlo simulation is a probabilistic approach.

3.5.2.5 Simulations

In the Markov cohort simulation, all hypothetical subjects are distributed to states based on initial transition probabilities at the first cycle. Subjects in each state (cohort) are relocated to states based on the transition probabilities at the second cycle. The process is repeated until it reaches the point of termination. The rewards are the sum of the number of cohort members in each state multiplied by the incremental utility for that state. Given the same inputs, a Markov cohort simulation always yields the same outputs, so it is deterministic. A Markov cohort simulation targets overall outcomes among states, while the first-order Monte Carlo simulation focuses on outcomes at the individual level.

The first-order Monte Carlo simulation models a subject's lifetime progression of disease (as a trial) based on probabilistic transition probabilities.[276] It is like a longitudinal study that follows each participant for his/her whole lifetime. It is commonly used in health analyses when a subject's historical experiences need to be included in the model. (Remember that Markov processes have no memory for previous cycles.) The rewards are calculated as the average time that all subjects spent at each state multiplied by the utility (effectiveness) of each state. Even given the same inputs,

276 Briggs, A. H. (2000). Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 17(5): 479-500.

this method may generate different outputs for each trial/simulation because of the randomization at chance nodes. Only if the number of simulations is large enough (at least thousands) will the average outputs from the first-order Monte Carlo simulation and outputs from the Markov cohort simulation reach similar results. Unlike the deterministic Markov cohort simulation, the probabilistic first-order Monte Carlo simulation can easily calculate statistics (such as the means, variance of error and confidence intervals) and handle uncertainty..[277]

3.5.2.6 Features of Markov Modeling

The advantages of using the Markov model include: (1) appropriate modeling of the state progression for conditions of glucocorticoid-induced osteoporosis and osteoporotic fractures; (2) Markov modeling can project long-term costs and clinical outcomes, and compare both outcomes at the same time for the cost-effectiveness study; and (3) uncertainty may be adequately addressed by performing probabilistic sensitivity analyses. Therefore, Markov modeling is the preferred method for this study. There are at least four components that must be explicitly described for a Markov model: (1) states and allowable transitions; (2) cycle length; (3) transition probabilities; and (4) method of simulations.

3.5.3 Specifications of the Study Model

A Markov model can model sequences of fractures where the probability of a fracture occurring depends upon the occurrence of a preceding fracture. A Markov

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277 Hunink, M. G. M. *et al.* (2001). Variability and uncertainty. In: Hunink, M. G. M.; Glasziou, P. P. (editors) *Decision Making in Health and Medicine*. The Press Syndicate of the University of Cambridge; Cambridge. Pages 339-363.

model with a Monte Carlo approach was used for generating long-term estimates of costs and effectiveness (osteoporotic fracture avoided), which were used in the decision analyses explained in Section 3.6. Deterministic analyses allow the projection of long-term estimates for the base cases. The first-order Monte Carlo simulation provides person-level estimates, and yields estimates of variance for averaged long-term estimates. The average costs from long-term estimations were compared. The hypotheses for the fifth study objective were tested by comparisons of the average costs among different treatment options. The second-order Monte Carlo simulations incorporate long-term estimates with variance in parameters and were used as a tool for probabilistic sensitivity analysis. The model specifications are explicitly stated in the following sections.

3.5.3.1 Model States, Allowable Transitions and Cycle Length

The Markov (state-transition) model will simulate the natural course of glucocorticoid-induced osteoporosis in glucocorticoid users at the initiation of glucocorticoid therapy through two-years, 10 years, lifetime (defined as the age of 99 years), a limited number of episodes of osteoporotic fracture (two episodes for two-year or 10-year estimations, three episodes for lifetime estimations) or death. The Markov health states for glucocorticoid users and allowable state transitions are illustrated in Figure 3.4. Five health states are proposed: (1) the "WELL" state where subjects have no symptoms; no prior experience with fractures and osteoporosis; (2) the "GIOP" state where subjects are diagnosed with glucocorticoid-induced osteoporosis without any prior fracture; (3) the "FX" state where glucocorticoid-induced osteoporotic fracture is diagnosed and subjects are being treated; (4) the "GIFX" state where subjects recover

from fractures and remain osteoporotic with a prior experience of fractures; and (5) the "DEAD" state.

All allowable transitions are not reversible (i.e., they are one-way), except between the "FX" and "GIFX" states. It means that once glucocorticoid-induced osteoporosis (or osteoporotic fracture) is developed and diagnosed, subjects cannot go back to the "WELL" state, which indicates no experience with osteoporosis and fractures. Basically, subjects in the "GIOP" and "GIFX" states are considered to have osteoporosis. The major difference is that subjects in the "GIOP" state have no prior experience in fractures, while those in the "GIFx" state experienced at least one episode of osteoporotic fractures. The "FX" state is treated as a tunnel state, and viewed as a process of fracture treatments. It is assumed that subjects will stay in the "FX" state for only one cycle (i.e., three months, see Section 3.5.3.2) and must enter to the "GIFX" state in the next cycle. Subjects in this state were treated for osteoporotic fractures. It is assumed that subjects receiving treatments for osteoporotic fractures will be recovered after one Markov cycle (i.e., three months).

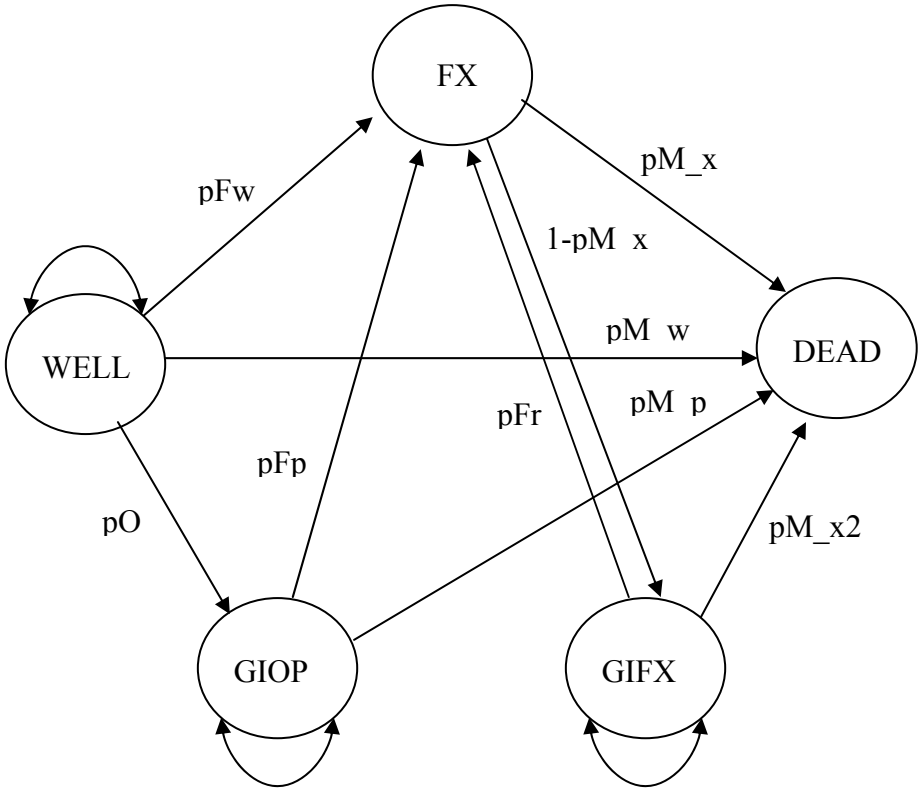
The cycle length of a Markov model usually depends upon the speed, progression and the nature of the condition/disease. The cycle length of Markov modeling for this study is three months, because glucocorticoid-induced bone loss occurs as early as three months after the initiation of glucocorticoid therapy. It is assumed that osteoporotic fractures occur at the end of the model cycle, so that half-cycle correction (HCC) is not used. At the end of model cycle: (1) subjects who entered the absorbed ("DEAD") state remain in the "Dead" state; (2) those who enter the "FX" state must enter the "GIFX" state; (3) those who are in the "WELL," "GIOP," or "GIFX" state may either stay in the same state or transit to another state based on transition probabilities which were obtained from descriptive statistics described in Section 3.2.3.

3.5.3.2 Transition Probabilities

As shown in Figure 3.4, a total of eight transition probabilities are needed for each treatment option in this Markov model. The descriptive analyses in Section 3.3 yield national estimates of age-specific annual incidence rates of osteoporosis and osteoporotic fractures. The annual rates (r) are converted to three-month transition probabilities (t =4) by the equation described in Section 3.5.2.2.

Therefore, the following transition probabilities can be obtained: (1) pO (from "WELL" state to "GIOP" state); (2) pFw (from "WELL" state to "FX" state); (3) pFp (from "GIOP" state to "FX" state); and (4) pFr (from "GIFX" state to "FX" state). In theory, osteoporotic fractures result from osteoporosis. When subjects in the "WELL" state develop osteoporotic fractures, they should go through the "GIOP" state, and reach "FX" state. In practice, glucocorticoid-induced osteoporosis may be under-diagnosed and/or the development of osteoporotic fractures is within three months (a model cycle). Subjects in the "WELL" state may skip the "GIOP" state and directly enter the "FX" state within one cycle.

$$p(4) = 1 - \exp(-4r)$$



Note:

WELL =subjects without prior osteoporosis and fracture.
FX =subjects experiencing any one of osteoporotic fractures.
DEAD =subjects are dead.
pFw =Probability of osteoporotic fractures from the WELL state
pO =Probability of osteoporosis from the WELL state
pFp =Probability of osteoporotic fractures from the GIOP state
pFr =Probability of osteoporotic fractures from the GIFX state

GIOP =subjects with prior osteoporosis but no prior fracture.
GIFX =subjects recovered from prior fracture.

pM_w =Probability of deaths from the WELL state
pM_x =Probability of deaths from the FX state
pM_p =Probability of deaths from the GIOP state
pM_x2 =Probability of deaths from the GIFX state

Figure 3.4 Markov health states for glucocorticoid tablet users

A totally different approach was used to estimate the other four mortality-related transition probabilities, pM_w, pM_p, pM_x and pM_x2. MEPS data do not yield information on mortality rates, so transition probabilities to the "DEAD" state need to be obtained from other sources. Osteoporosis-related mortality rates were obtained from

the literature review on mortality due to osteoporosis and osteoporotic fractures in glucocorticoid users (Section 2.3.3). Because there is no information on differences in mortality among different anti-osteoporotic treatments in glucocorticoid users, the mortality rates are assumed to be the same. Table 3.5 summarizes three-month transition probabilities for mortality which were converted from the annual rates.

The pM_w (WELL-to-DEAD) in the control group is estimated by using the crude mortality rate of low-dose glucocorticoid users with rheumatoid arthritis (RA). The pM_w in the treatment groups were estimated by multiplying the pM_w in control group by 0.34 which is the odds ratios of mortality rates in osteoporosis-treated patients to untreated patients.[278] The same estimation applies to other probabilities of mortality (pM_p, pM_x and pM_x2) between the control group and the treatment groups (as indicated by "f" in note column of Table 3.5). These mortality rates were obtained from previous studies including different target populations (e.g., different underlying conditions and different glucocorticoid use), so sensitivity analysis was performed to vary transition probabilities of mortality.

278 Cree, M. W. *et al*. (2003). Mortality and morbidity associated with osteoporosis drug treatment following hip fracture. *Osteoporosis International* 14(9): 722-727.

Table 3.5 Three-month mortality rates for the base case in female glucocorticoid users

State*	WELL to DEAD			FX to DEAD			GIOP to DEAD			GIFX to DEAD		
Option**	Age	3-m Prob.	Note	Age	3-m Prob.	Note	Age	3-m Prob.	Note	Age	3-m Prob.	Note
Female												
CT	60	**.0032**	a	60	**.0384**	b, c	60	**.0014**	d, e	60	**.0080**	d, e
				80	**.1236**	b, c	80	**.0028**	d, e	80	**.0184**	d, e
BP, CN, HT, HB, RF	60	**.0011**	f	60	**.0131**	f	60	**.0005**	f	60	**.0027**	f
				80	**.0420**	f	80	**.0010**	f	80	**.0063**	f
Male												
CT	60	**.0032**	a	60	**.0759**	b, c	60	**.0374**	g	60	**.0759**	h
				80	**.2964**	b, c	80	**.1179**	g	80	**.2964**	h
BP, CN, HT, HB, RF	60	**.0011**	f	60	**.0258**	f	60	**.0127**	f	60	**.0027**	f
				80	**.1007**	f	80	**.0400**	f	80	**.0063**	f

*WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures;

**BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene group;

a. The crude mortality rate of RA patients with glucocorticoid use less than 10 years is 12.3% or 60.5% for more than 10-year glucocorticoid therapy, Sihvonen *et al.* (2006) *J Rheumatology* 33(9): 1740-1746.

b. Age-adjusted mortality rates (converted to 3-month probabilities) within one year after fractures in the general population in Sweden; Johnell *et al.* (2004) *Osteoporosis Int* 15: 38-42.

c. The hazard risk of deaths after one-year glucocorticoid treatment in RA patients is 1.14 (95% CI 0.98-1.27); for 10-year GS treatment it is 1.69 (95% CI 1.12-2.56); Sihvonen *et al.* (2006) *J Rheumatology* 33(9): 1740-1746.

d. Compared to no glucocorticoid use, the adjusted relative risk of mortality in severe COPD patients with 10 mg glucocorticoid use is 2.34 (95% CI 1.24-4.43); Schds *et al.* (2001) *Eur Respir Journal* 17: 337-342.

e. The crude mortality rate in post menopausal women with BMD t-score < -1.5 is 4.7/1,000 person-years, or 27.89/1,000 person-years in women with prior fracture; Causley *et al.* (2000) *Osteoporosis Int* 11: 556-561.

f. The odds ratio of long-term mortality is 0.34 (95% CI 0.17-0.70) for some osteoporosis treatment after hip fracture; Cree *et al.* (2003) *Osteoporosis Int* 14:722-727

g. No data are available in men for estimation. Assume a 50% decrease from those in the FX state.

h. No data are available in men for estimation. Assume the same as those in the FX state.

Age-specific mortality rates within one year after fractures in the general population were reported by Johnell *et al.*[279] Mortality rates after osteoporotic fractures were also reported in men by Center *et al.*[280] The hazard risk of deaths after one year of

279 Johnell, O. *et al.* (2004). Mortality after osteoporotic fractures. *Osteoporosis International* 15(1): 38-42.

280 Center, J. R. *et al.* (1999). Mortality after all major types of osteoporotic fracture in men and women: an observational study. *The Lancet* 353(9156): 878-882.

glucocorticoid treatment in RA patients is 1.69 (95% CI 1.12-2.56) for 10-year glucocorticoid treatment.[281] The pM_x (FX-to-DEAD) in the control group was estimated by multiplying age-specific mortality rates by 1.69.

The crude mortality rate in post menopausal women with BMD t-score < -1.5 is 4.7 per 1,000 person-years or 27.89 per 1,000 person-years in women with prior fractures.[282] Compared to no glucocorticoid use, the adjusted relative risk of mortality in COPD patients who received daily 10 mg oral prednisone equivalents for at least six months is 2.34 (95% CI 1.24-4.43).[283] The pM_p and pM_x2 (GIOP-to-DEAD and GIFX-to-DEAD) in women were estimated by multiplying the crude mortality rates by 2.34. For pM_p in men, no data were available for estimates, so a 50% decrease in mortality rates after fractures in men are assumed (as indicated by "g" in note column of Table 3.5). For pM_x2 in men, no data were available for estimates, so the same mortality rates as men in the FX state are assumed (as indicated by "h" in note column of Table 3.5).

3.5.3.3 Example of Decision Tree and Markov Information

The decision-tree of the Markov model for bisphosphonates as an example is illustrated in Figure 3.5. Other therapeutic options include calcitonin (CN), control group (CT), combination of hormone replacement and bisphosphonate therapy (HB), hormone replacement therapy (HT), and raloxifene (RF). All share a structure similar to

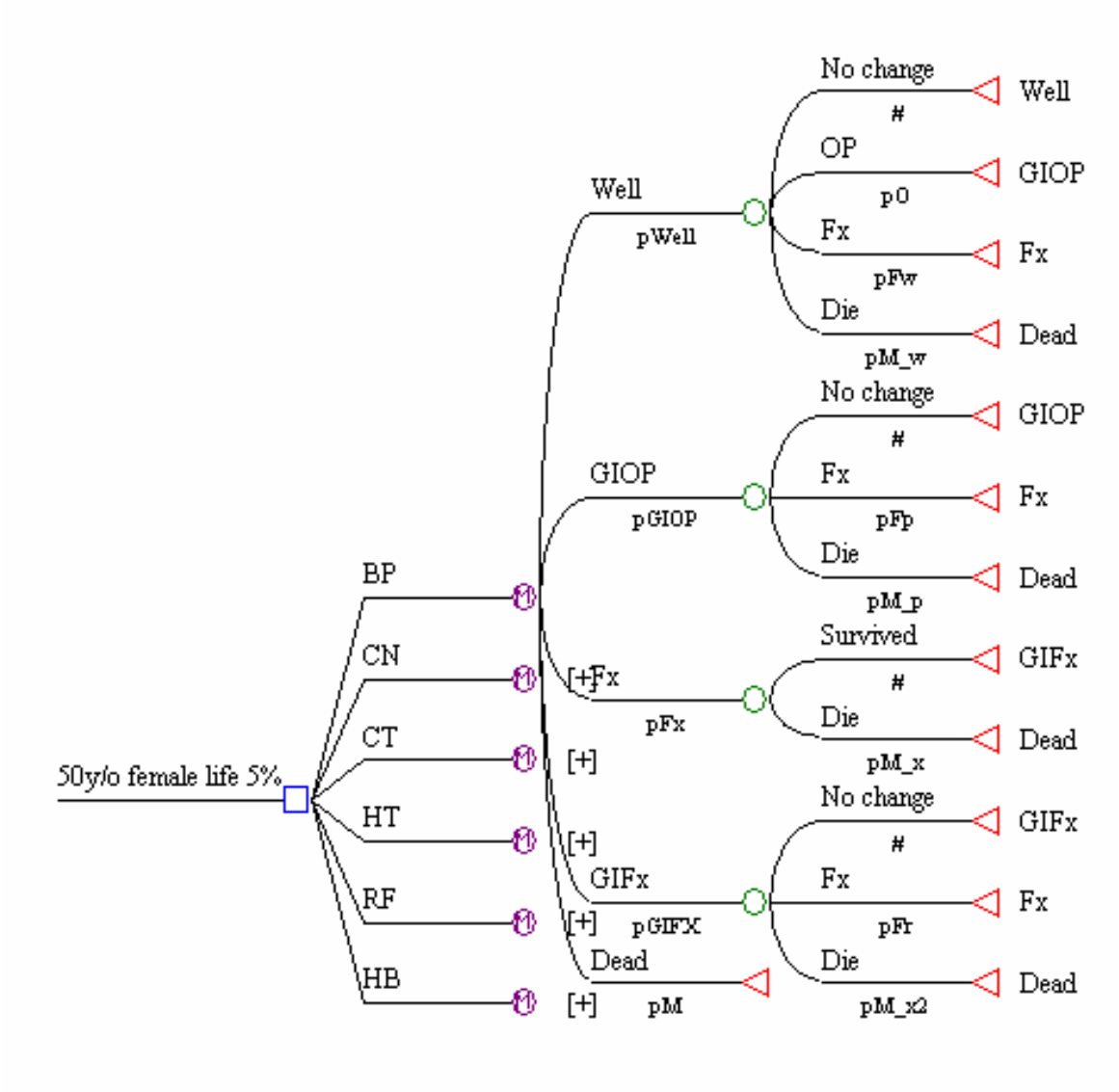
281 Sihvohen, S. *et al.* (2006). Mortality in patients with rheumatoid arthritis treated with low-dose oral glucocorticoids. a population-based cohort study. *Journal of Rheumatology*, 33(9): 1740-1746.

282 Cauley, J. A. *et al.* (2000). Risk of mortality following clinical fractures. *Osteoporosis International* 11(7): 556-561.

283 Schols, A. M. W. J. *et al.* (2001). Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *European Respiratory Journal*, 17(3): 337-342.

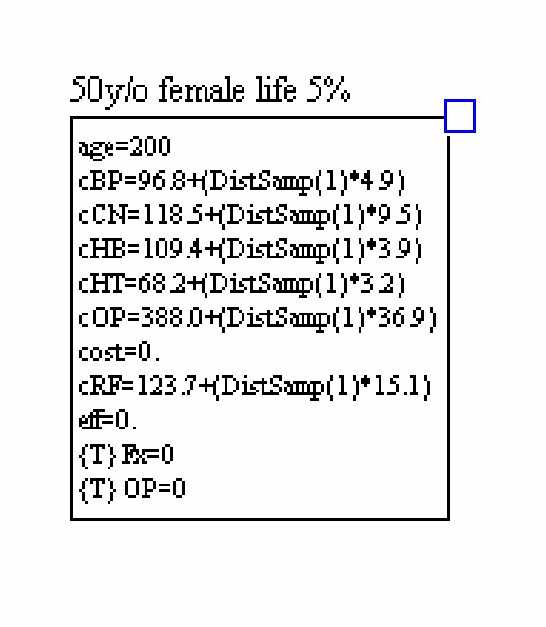
the bisphosphonate option, but have different transition probabilities and outcomes in the decision tree. Decision analyses with Markov modeling allows long-tern projections and yields rewards for all options simultaneously.

A set of parameters in Markov modeling is described below as an example of base cases for a cohort of female glucocorticoid users aged 50 years old who receive bisphosphonate (BP) treatment. Figure 3.6 illustrates parameter settings for all options in the decision tree by using this cohort as an example. The inputs of costs are obtained from results of descriptive analyses described in Section 5.3. A randomly generated probability based on the normal distribution [DistSamp (1), mean=0, standard deviation=1] was used to introduce variance for the average costs. Figure 3.7 and Figure 3.8 illustrate an example of Markov information (i.e., parameter settings in Markov modeling), including initial status, criterion for termination of Markov cycles, reference for transition probabilities and assignment of rewards (i.e., costs and effectiveness gained after each cycle), for the bisphosphonate (BP) branch of the decision tree. A randomly generated probability based on the triangular distribution [DistSamp (2), min.=0.7, likeliest=1, max.=1.3] was used to introduce variance for the transition probabilities.



Note:
BP =bisphosphonate; **CN** =calcitonin; **CT** =controls; **HT** =hormone replacement therapy; **RF** =raloxifene;
HB =combined use of BP & HT; **y/o** =years old; 5%=annual discount rate of 5%
pWELL, pGIOP, pFX, pGIFX=initial distribution of subjects in each state;
WELL =subjects without prior osteoporosis and fracture. **GIOP** =subjects with prior osteoporosis but no prior fracture.
FX =subjects experiencing any one of osteoporotic fractures. **GIFX** =subjects recovered from prior fracture.
DEAD =subjects are dead.
pFw =Probability of osteoporotic fractures from the WELL state **pM_w** =Probability of deaths from the WELL state
pO =Probability of osteoporosis from the WELL state **pM_x** =Probability of deaths from the FX state
pFp =Probability of osteoporotic fractures from the GIOP state **pM_p** =Probability of deaths from the GIOP state
pFr =Probability of osteoporotic fractures from the GIFX state **pM_x2** =Probability of deaths from the GIFX state

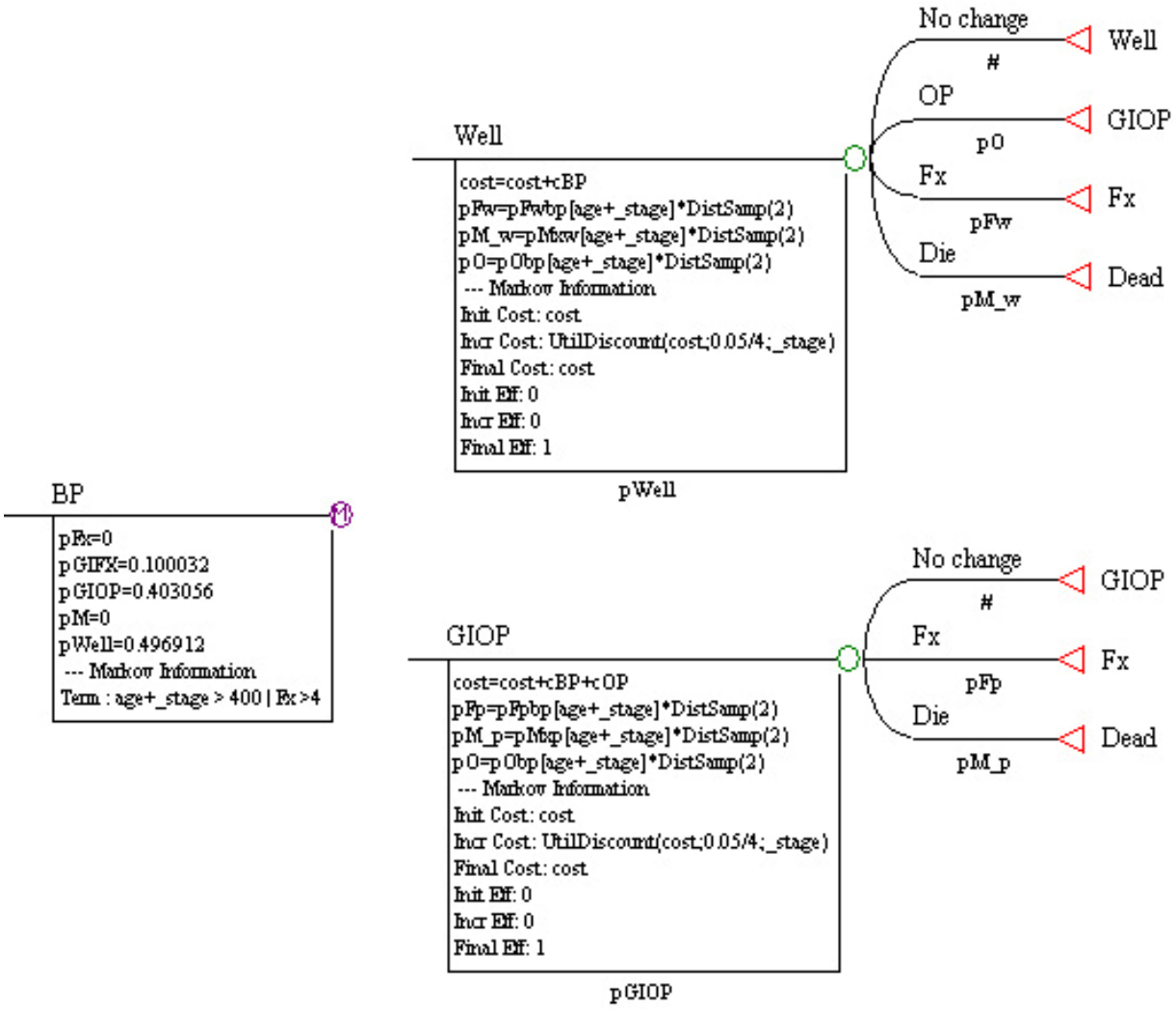
Figure 3.5 Decision tree with Markov modeling by showing the bisphosphonate subtree for a 50-year-old female cohort as an example



Note:

y/o =years old; 5%=annual discount rate of 5%
Age= initial age, converted to number of Markov cycles
Cost =average costs± multiplier times standard deviation
Eff =effectiveness (fracture avoided)
DistSamp(1)= a random value based on a normal distribution.
cBP=3-month costs for bisphosphonate treatment
cHB=3-month costs for combined use of BP and HRT
cCN=3-month costs for calcitonin treatment
cHT=3-month costs for hormone replacement therapy
cRF=3-month costs for raloxifene treatment
cOP=3-month costs for monitoring osteoporosis
{T}Fx=cumulative number of osteoporotic fractures
{T}OP=cumulative number of osteoporosis

Figure 3.6 Parameter settings in the decision tree for a cohort of 50 year-old women



Note:

BP =bisphosphonate; **y/o** =years old; 5%=annual discount rate of 5%

pWELL, pGIOP, pFX, pGIFX=initial distribution of subjects;

DistSamp(2)= a triangular distribution: ± 30% of variance, minimum=0.7, likeliest=1, maximum=1.3

WELL =subjects without prior osteoporosis and fracture.

GIOP =subjects with prior osteoporosis but no prior fracture.

FX =subjects experiencing any one of osteoporotic fractures.

GIFX =subjects recovered from prior fracture.

Cost =total costs

Eff =effectiveness (fracture avoided)

cBP=3-month costs for bisphosphonate treatment

cOP=3-month costs for monitoring osteoporosis

pFw =Probability of osteoporotic fractures from the WELL state

pM_w =Probability of deaths from the WELL state

pO =Probability of osteoporosis from the WELL state

pM_x =Probability of deaths from the FX state

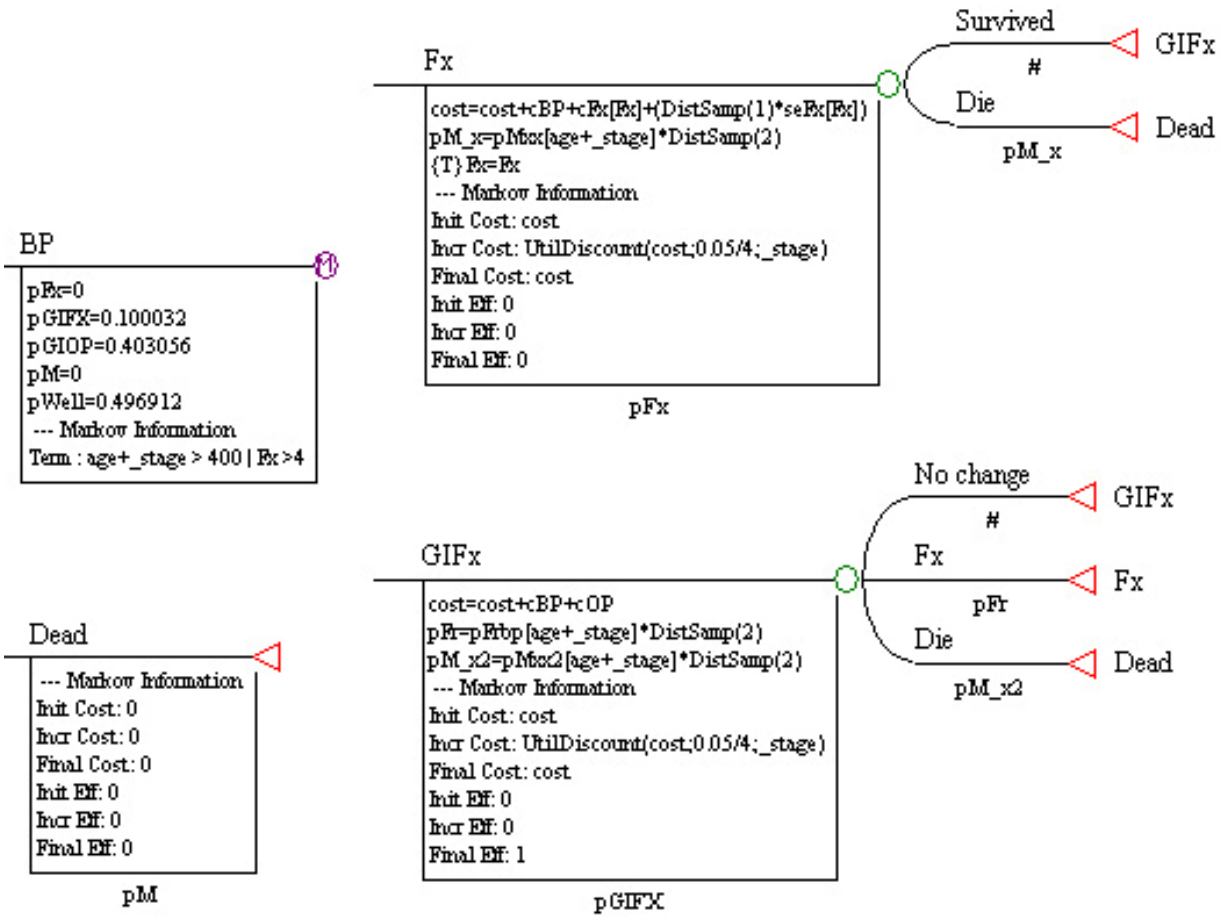
pFp =Probability of osteoporotic fractures from the GIOP state

pM_p =Probability of deaths from the GIOP state

pFr =Probability of osteoporotic fractures from the GIFX state

pM_x2 =Probability of deaths from the GIFX state

Figure 3.7 Markov information for the WELL and GIOP states for the bisphosphonate option in the decision tree



Note:

BP =bisphosphonate; **y/o** =years old; 5%=annual discount rate

pWELL, pGIOP, pFX, pGIFX=initial distribution of subjects

DistSamp(2)= a triangular distribution: ± 30% of variance, minimum=0.7, likeliest=1, maximum=1.3

WELL =subjects without prior osteoporosis and fracture.

GIOP =subjects with prior osteoporosis but no prior fracture.

FX =subjects experiencing any one of osteoporotic fractures.

GIFX =subjects recovered from prior fracture.

Cost =total costs

Eff =effectiveness (fracture avoided)

cBP=3-month costs for bisphosphonate treatment

cOP=3-month costs for monitoring osteoporosis

pFw =Probability of osteoporotic fractures from the WELL state

pM_w =Probability of deaths from the WELL state

pO =Probability of osteoporosis from the WELL state

pM_x =Probability of deaths from the FX state

pFp =Probability of osteoporotic fractures from the GIOP state

pM_p =Probability of deaths from the GIOP state

pFr =Probability of osteoporotic fractures from the GIFX state

pM_x2 =Probability of deaths from the GIFX state

Figure 3.8 Markov information for the FX, GIFX and DEAD states for the bisphosphonate option in the decision tree

3.5.3.4 Monte Carlo Simulations

A simulation method must be used for a Markov model to project long-term estimates. The Markov cohort analysis and Monte Carlo simulations are two commonly used approaches which were briefly described earlier in Section 3.5.2.5. There are two important features of the Monte Carlo method which makes it the preferred approach for this study. The first-order Monte Carlo simulation can yield the estimation of variance (which will be presented as confidence intervals) of expected values/rewards for each state so uncertainty of sampling variation could be evaluated (see Section 3.5.4). The first-order simulation helps address uncertainty at the individual level.

The first-order Monte Carlo simulations were performed for the cohort of 10,000 hypothetical glucocorticoid users. All hypothetical patients start from the "WELL" state at the beginning of the first cycle. Results of analyses for base cases (also called "reference cases") were reported because it has been suggested by the U.S. Panel on Cost-effectiveness in Health and Medicine.[284, 285, 286] The base cases for this study were hypothetical male or female cohorts at ages of 30 years old, 50 years old and 65 years old. Model inputs of costs and effectiveness were derived from results of descriptive analyses without introducing estimation of variance. Rewards (means of costs and effectiveness) and standard deviations were calculated based on 10,000-sample simulations. These rewards were treated as long-term estimates for costs and effectiveness. Rewards were compared among different anti-osteoporotic treatments,

284 Weinstein, M. C. *et al.* (1996). Recommendations of the panel on cost-effectiveness in health and medicine. *Journal of the American Medical Association* 276(15): 1253-1258.
285 Siegel, J. E. *et al.* (1996). Recommendations for reporting cost-effectiveness analyses. panel on cost-effectiveness in health and medicine. *Journal of the American Medical Association* 276(16): 1339-1341.
286 Russell, L. B. *et al.* (1996). The role of cost-effectiveness analysis in health and medicine. panel on cost-effectiveness in health and medicine. *Journal of the American Medical Association* 276(14): 1172-1177.

and hypotheses for the fifth study objective were tested. Information on rewards is also presented as cost-effectiveness ratios (C/E) or an incremental cost-effectiveness ratio (ICER), which means the cost to prevent an additional fracture (e.g., the cost per avoided fracture). These pieces of information were used in the cost-effectiveness analyses in Section 3.6.

The second-order Monte Carlo simulation introduces estimation of variance at the parameter level. Additionally, the variables that potentially influence the transition probabilities can be varied simultaneously. Probabilistic/stochastic sensitivity analyses on these variables can be performed at the same time by using the second-order Monte Carlo simulation. Therefore, parameter uncertainty can be evaluated. The next section highlights the basic concepts and theories about uncertainty related to cost-effectiveness analyses.

3.5.4 Handling Uncertainty

There are four sources of uncertainty in cost-effectiveness analytical models. (1) Methodological uncertainty comes from the disagreement among analysts who used different analytical methods in terms of definition, inclusion, measurements and valuation of outcomes in the analysis, so the study results may not be directly comparable. (2) Parameter uncertainty refers to uncertainty of model inputs (parameters). Sampling variation from different inclusion/exclusion criteria and sample characteristics is also classified as parameter uncertainty. (3) Modeling uncertainty includes uncertainty due to model structure and the whole modeling process. (4) Generalizability implies the uncertainty of extrapolating study results to the target population in general. [287, 288]

287 Briggs, A. H. (2000). Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 17(5): 479-500.

Basically, model analysts must explicitly describe study methods in detail so that the above sources of uncertainty can be identified accordingly. The use of a "reference case" of core methods is advocated for handling methodological uncertainty, and makes possible comparisons of results among studies using different analytical methods. Some statistical methods are highlighted as follows to estimate uncertainty for stochastic analyses.

3.5.4.1 Confidence Intervals

Confidence intervals (CIs) for ICERs are frequently reported to indicate uncertainty. There are five common methods. The first method is the confidence box, where the upper and lower limits of the confidence intervals on cost and effectiveness are based on standard parametric statistics. For example, when α =0.05, 95% confidence interval of utility is formulated as:[289]

$$C.I. = \Delta\overline{U} \pm 1.96 \times Se = \Delta\overline{U} \pm 1.96 \times \sqrt{\frac{s^2 a}{n_a} + \frac{s^2 b}{n_b}}$$

where ΔU is the incremental difference between two alternatives, Se is the standard error of the difference, s^2 is the estimated variance from the sample, and n is the sample size.

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288 Briggs, A. H. (2001). Handling uncertainty in economic evaluation and presenting the results. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care*; Oxford University Press, New York. Pages 172-214.

289 Briggs, A. H. (2001). Handling uncertainty in economic evaluation and presenting the results. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care;* Oxford University Press, New York. Pages 172-214.

The two limits of ICERs are $(\frac{\Delta\overline{C} - 1.96Se}{\Delta\overline{E} + 1.96Se})$ and $(\frac{\Delta\overline{C} + 1.96Se}{\Delta\overline{E} - 1.96Se})$, respectively. However, the chance of simultaneously considering both cost and effectiveness CI is $(1-\alpha)^2$, when cost is independent of effectiveness. If α =0.05, the two limits of ICERs actually represent the 90.25% CI, instead of the 95% CI. Using this method to represent uncertainty is misleading.

The second method is the Delta method or the Taylor series approximation of the variance. One assumption of this method requires normally distributed data. The Taylor approximation incorporates the covariance between the cost and effectiveness of the ICER. However, given the highly skewed data of health care costs in most health analyses, the Taylor approximation should be used cautiously.

The third method is the confidence ellipse. It was proposed that the costs and effectiveness follow a joint normal distribution. The locus of points of the "joint density" is assumed to be elliptical in shape. The confidence ellipse method accounts for covariance between cost and effectiveness, but the correlation of cost and effectiveness has a big impact on the elliptical contour lines, which may result in incorrect confidence limits.

The fourth method is the Fieller's theorem. The advantage of this method is that it accounts for the potentially skewed distribution of ratio statistics. Therefore, the confidence ellipse may not be symmetric. However, the Fieller's theorem assumes $\Delta C - R \times \Delta E$ (where $R = \frac{\Delta\overline{C}}{\Delta\overline{E}}$) is normally distributed around zero; the skewness of health care costs may still violate the assumption.

The fifth method is non-parametric bootstrapping. Instead of assuming a normal distribution, the sample distribution of the ICER statistic is created by re-sampling from the original data. The confidence limits are derived by using a straightforward

percentile method: (α/2)100 and (1-α/2)100 percentiles. However, if the two extreme ends of the distribution have relatively high frequency (for example, the ICER is close to zero when costs are similar and the ICER is close to infinity when effectiveness is similar), the bootstrap method is misleading. Of these five methods, Fieller's method and the bootstrap method are often recommended, and Taylor series approximation is frequently used.[290] This study used the SAS SURVEYMEANS procedure, which uses the Taylor series approximation to calculate the variance of weighted means.

3.5.4.2 Sensitivity Analyses

In addition to confidence intervals, sensitivity analysis is another useful tool to provide possible results by varying factors (parameters, process, criteria, etc.) associated with uncertainty, so decision makers have more information on strategy selection. Sensitivity analyses may also be classified as either deterministic or probabilistic. The deterministic n-way sensitivity analysis assesses the robustness of model outcomes by varying values of n parameters. However, when the parameters are more than two, the use of this deterministic sensitivity analysis becomes burdensome. Uncertainty exists in estimates of costs and transition probabilities in the study model. To handle uncertainty for these parameters simultaneously, probabilistic sensitivity analysis was selected for this study.

Second-order Monte Carlo simulation is a tool for a probabilistic sensitivity analysis. Second-order Monte Carlo simulation assesses the impact on model outcomes by varying values of multiple parameters simultaneously and can be used in the Markov

290 Briggs, A. H. (2001). Handling uncertainty in economic evaluation and presenting the results. In: Drummond, M. F.; McGuire, A. (editors) *Economic Evaluation in Health Care*; Oxford University Press, New York. Page 191.

cohort analysis or the first-order Monte Carlo simulation.[291] The probabilistic second-order Monte Carlo simulation addresses the issue of parameter uncertainty, and simultaneously considers different types of probability distributions for different parameters.[292] For example, a gamma (log-normal) distribution could be used to describe positively skewed health care cost data; a triangular or beta distribution could be used to represent probabilities which are bounded between zero and one. When probabilities are obtained directly from original data, Bayesian methods could be used.

A Bayesian approach to stochastic (probabilistic) sensitivity analysis were used for selected variables to assess uncertainty on the levels of sampling and parameters.[293, 294, 295, 296, 297] The variables include, but are not limited to, sampling variance, rewards and transition probabilities. Because descriptive analyses yield means and standard deviations for cost estimates, a normal distribution was used to describe uncertainty of cost estimates. A triangular distribution ($\pm$ 30% of variance, minimum=0.7, likeliest=1, maximum=1.3) was used to represent transition probabilities which are bounded between zero and one.

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291 Briggs, A. H. (2000). Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 17(5): 479-500.

292 Hunink, M. G. M. *et al.* (2001). Variability and uncertainty. In: Hunink, M. G. M.; Glasziou, P. P. (editors) *Decision Making in Health and Medicine*. The Press Syndicate of the University of Cambridge; Cambridge. Pages 339-363.

293 Felli, J. C. & Hazen, G. B. (1999). A Bayesian approach to sensitivity analysis. Health Economics 8(3): 263-268.

294 Briggs, A. H. (1999). A Bayesian approach to stochastic cost-effectiveness analysis. *Health Economics* 8(3): 257-261.

295 Heitjan, D. F. *et al.* (2004). Bayesian estimation of cost-effectiveness from censored data. *Statistics in Medicine* 23(8): 1297-1309.

296 Heitjan, D.F. & Li, H. (2004). Bayesian estimation of cost-effectiveness: an importance-sampling approach. *Health Economics* 13(2): 191-198.

297 Cooper, N. J. *et al.* (2004). Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. *Health Economics* 13(3): 203-226.

3.6 COST-EFFECTIVENESS ANALYSES

This section covers cost-effectiveness analysis which addresses the sixth study objective. The long-term estimates of costs and effectiveness were obtained from the results of Markov modeling with the first-order Monte Carlo simulations for each option of anti-osteoporotic treatments, including the control group. The incremental cost-effectiveness ratios (ICERs) of these long-term estimates were calculated for each option of the anti-osteoporotic agents compared with glucocorticoid users who did not use any anti-osteoporotic agent (the control option). The second-order Monte Carlo simulation yielded estimates for probabilistic sensitivity analyses.

The confidence levels of the ICER can be interpreted by the cost-effectiveness acceptability curve which facilitates decision making.[298] The cost-effectiveness acceptability curve provides an estimate of the probabilities that the true ICER is less than the value of the ceiling ratio (i.e., willingness-to-pay, WTP).[299, 300, 301] This allows a simultaneous comparison of all possible alternatives in one plot. It also allows checks of hypotheses for the sixth study objective where ICER of each option is compared to the ceiling ratios (i.e., WTP). By using the cost-effectiveness acceptability curve, different decision makers may find the corresponding range of probabilities that remain cost-effective based on personalized willingness-to-pay.

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298 Lothgren, M. & Zethraeus, N. (2000). Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Economics* 9(7): 623-630.

299 Fenwick, E. *et al.* (2001). Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics* 10(8): 779-787.

300 Fenwick, E. *et al.* (2004). Cost-effectiveness acceptability curves -facts, fallacies and frequently asked questions. *Health Economics* 13(5): 405-415.

301 Negrin, M. A. & Vazquez-Polo, F. J. (2006). Bayesian cost-effectiveness analysis with two measures of effectiveness: the cost-effectiveness acceptability plane. *Health Economics* 15(4): 363-372.

3.7 OTHER CONSIDERATIONS

3.7.1 General Assumptions

In addition to assumptions mentioned in previous sections, several general assumptions are made for this study. The study results should still reflect actual patient experience given these assumptions. Some assumptions are made because of limitations of data. There are a total of nine general assumptions. Some assumptions which specifically relate to Markov modeling are described in Section 3.5 (Longitudinal Projection).

(1) **Diagnosis.** It is assumed that glucocorticoid-induced osteopenia, osteoporosis and osteoporotic fractures were fully identified in MEPS subjects during the data collection, and that these conditions are fully detected in hypothetical subjects for the modeling. There is no information available to estimate the degree of non-diagnosis. Even though osteoporosis is under-diagnosed, the ICD-9-CM codes reported in MEPS will still be used to estimate incidence of osteoporosis. The study results may still reflect the reality of under-diagnosis.

(2) **Label and off-labeled use.** It is assumed that all study subjects used bisphosphonates based on the FDA-approved regimens for glucocorticoid-induced osteoporosis, and used other anti-osteoporotic agents by following regimens for postmenopausal osteoporosis. Only FDA-approved agents for osteoporosis are considered for this study.

(3) **Switches, combination use and prior use of medications.** Switches between anti-osteoporotic agents are possible but switches are not considered in this study. Except for the bisphosphonate-HRT combination, subjects who reported more than one anti-osteoporotic agent are excluded in this study. The main reason is that it is

difficult to compare and interpret the "pure" cost-effectiveness of an anti-osteoporotic medication to another if medication switches and combination use were included. However, no information is available for switches and combination use beyond the periods of data collections for MEPS. The protective effects of anti-osteoporotic agents on bone loss may continue if subjects used any of the anti-osteoporotic agents before, but this study excludes subjects who reported use of anti-osteoporotic agents for less than three months. The carry-over effects are unlikely to be present for qualified study subjects. Nevertheless, it is assumed that there is no carry-over effect for qualified study subjects.

(4) **Adherence.** The issues of compliance for use of anti-osteoporotic agents have been discussed in the literature; however, compliance with and duration of each therapy were not explicitly stated in most studies.[302, 303] Evidence shows that compliance with therapy has an impact on cost-effectiveness. For example, a study reported that 20% improvement in persistence with bisphosphonates decreases fractures by 6 percent.[304] Even though the issue of compliance is important to evaluation of cost-effectiveness of anti-osteoporotic treatments, this study reflects the reality based on the study data. It is assumed that the pattern of imperfect compliance in the use of anti-osteoporotic agents remains the same for study subjects if they continue to use the same anti-osteoporotic agent beyond the period of data collection. This assumption allows projections of long-term estimates by the Markov modeling for hypothetical

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302 Cranney, A. *et al*. (1999). A review of economic evaluation in osteoporosis. *Arthritis Care and Research* 12(6): 425-434.

303 Coyle, D. *et al*. (2000). Cost-effectiveness research in osteoporosis. *Drug Development Research* 49(3): 135-140.

304 van den Boogaard, C. H. A. *et al.* (2006). Persistent bisphosphonates use and the risk of osteoporotic fractures in clinical practice: a database analysis Study. *Current Medical Research and Opinions*, 22(9): 1757-1764.

subjects with "imperfect" compliance. Therefore, the results of long-term projections reflect the "real-world" situations that patients may not totally comply with prescribed dosing regimens of anti-osteoporosis therapy. Additionally, because intermittent use of glucocorticoid steroids does not reduce bone loss and because the cumulative glucocorticoid dose is more important than lengths of glucocorticoid therapy, the impact of non-adherence with glucocorticoid therapy on risk of osteoporotic fractures is ignored.

(5) **Adverse drug reactions.** The adverse drug reactions due to use of anti-osteoporotic agents were included in calculations of total costs for anti-osteoporotic treatments in this study. However, to simplify the structure of the decision tree in Markov modeling, it was assumed that the adverse drug reactions do not alter the transition probabilities among Markov states in the study model. Besides the bone loss, other adverse reactions of glucocorticoid use were assumed to be equally distributed among users so they could be ignored.

(6) **Underlying conditions.** The impact of the underlying diseases on osteoporotic fractures was assumed to be equal between glucocorticoid users who used anti-osteoporotic agents and those who did not (the controls). Although different underlying diseases may have different impacts on the fracture rates as described in Chapter Two, it is not feasible to include all underlying diseases and categorize them into appropriate groups. Even if categories could be formed and study samples could be grouped into these categories, the sample size in each group (for each disease state) would be too small to generate meaningful national estimates for statistical analyses, which is an important study objective.

(7) **Causal relations**. It is assumed that all osteoporosis and osteoporotic fractures which occurred after the use of glucocorticoids are glucocorticoid-induced. Even though many other confounding factors (such as age, underlying diseases, etc.) may

have impacts on osteoporosis and osteoporotic fractures, glucocorticoid use is the most important factor for the study outcomes. Even though study outcomes may be influenced by many confounding factors, the effects from anti-osteoporotic treatments play a most cost-effective role on the overall study outcomes.

(8) **Limited number of episodes for osteoporotic fractures.** For the simplicity of the study models, each individual is limited to a maximum of two episodes of osteoporotic fractures in two-year or 10-year simulations, and a maximum of three episodes of osteoporotic fractures in lifetime simulations. This information was included in the criteria for Markov termination. The probability of having four or more osteoporotic fractures is believed to be relatively low in the general population; therefore, these rates were ignored in the study model. It is also assumed that any reported fracture in MEPS data is the subject's first fracture, unless more than one fracture was reported.

(9) **Longitudinal projection.** Using glucocorticoid steroids at a cumulative dose of 450 mg of prednisone or its equivalent is defined as high-risk glucocorticoid use. Once an individual starts long-term glucocorticoid therapy or anti-osteoporosis treatment, he or she is assumed to use it continuously by following the same pattern for the rest of his or her lifetime. This assumption allows for the projection of long-term outcomes (costs and fracture rates) from the short-term data.

3.7.3 Ethical Consideration

The study was approved by the University of Texas Institutional Review Board (IRB) on February 8th, 2007. The IRB protocol number is #2007-01-0094. This study has minimal risk regarding privacy and confidentiality. The letter of approval is included in Appendix A.

This project involves the collection of existing datasets (MEPS) which are publicly available and governed by the Agency for Healthcare Research and Quality (AHRQ). Because personal identifiers have been removed from the public-access datasets in MEPS by the AHRQ, subjects cannot be identified directly or indirectly through identifiers linked to the subjects. Additionally, this study is a retrospective database analysis. Study subjects were not physically involved in the research project and there was no interaction between the researcher and survey participants. This study has no impact on therapies that has been received or will be received by the study subjects. Therefore, no informed consent can be obtained or applied to this project.

3.8 SUMMARY OF CHAPTER THREE

The use of "real-world" data is one of the important keys to this study, so the study datasets were described at the beginning of this chapter. A retrospective analysis of data from the 1996-2004 MEPS was conducted to yield nationally representative, "real-world" estimates of clinical and economic outcomes for this study. Analysis of variance was used to compare means of these estimates among anti-osteoporotic treatment groups. Logistic regression analysis was used to to estimate relative risks of osteoporotic fractures in long-term glucocorticoid users in comparison to non-glucocorticoid users. Markov modeling with Monte Carlo simulations was used to yield long-term estimates of cost-effectiveness for each anti-ostoeporotic treatment. Cost-effectiveness analysis was used to compare long-term estimates of cost-effectiveness of anti-osteoporotic treatments. A brief review of therories and concepts was provided for cost-effectiveness analyses and the Markov modeling technique.

There were a total of six groups of anti-osteoporotic treatments: bisphosphonate therapy (BP), calcitonin therapy (CN), hormone replacement therapy (HT), the combined use of HRT and bisphosphonates (HB), raloxifene therapy (RF) and the control group (CT). Calcium and vitamin D products were excluded as a comparison group because they were assumed to be provided to all study subjects. Teriparatide has been available since 2003. Because teriparatide was not used by any glucocorticoid user who was qualified for this study, it was not included in this study.

CHAPTER FOUR-RESULTS

This chapter consists of five sections which present study results according to study objectives. Section 4.1 summarizes and compares average ages and glucocorticoid use of study subjects among different treatment groups. Section 4.2 shows national estimates of incidence rates of osteoporosis and osteoporotic fractures in subjects categorized by gender and different types of glucocorticoid use. Section 4.3 shows national estimates of average direct medical costs associated with osteoporosis, osteoporotic fractures and different treatments. Because these estimates of costs and fracture rates are based on 2-year follow-ups for each individual in the Medical Expenditure Panel Survey (MEPS), they are treated as "short-term" outcomes. Section 4.4 describes inputs of Markov modeling, and demonstrates estimated "long-term" outcomes for cohorts with different characteristics. Section 4.5 compares "short-term" and "long-term" cost-effectiveness across different treatment options, and suggests the best option for patients in different cohorts.

4.1 STUDY SUBJECTS

The first section describes study subjects by providing descriptive statistics of important characteristics which may have an impact on study outcomes. These characteristics include gender, age, glucocorticoid use and the underlying conditions for which glucocorticoid tablets were prescribed. They are compared among subjects categorized by duration and amount of glucocorticoid use. These characteristics are further compared among subjects with different treatments. When a significant difference in any of these important characteristics is found, it indicates the characteristic evaluated has an impact on costs and effectiveness of anti-osteoporotic treatments.

Study outcomes should be compared among anti-osteoporotic treatments with caution in this chapter. The results from this section address the first study objective.

4.1.1 Glucocorticoid Users

First of all, subjects in the Medical Expenditure Panel Survey (MEPS) from 1996 to 2004 are summarized in Table 4.1.1, which shows unweighted and weighted number and average ages of subjects by year and gender. The average unweighted numbers of subjects is 30,253 per year, the weighted average age is 35.6 years old and 51.1% of them are female. Female subjects are older than male subjects (weighted average age of women: 36.7 years old, men: 34.5 years old; df=1, F=627.38, $p<0.0001$). It is estimated that 4.5% (12,663,459/280,566,064) of the non-institutional U.S. population are oral glucocorticoid tablet users at any dose and length of therapy; the percentages are 3.7% (5,075,366/137,088,576) in men and 5.3% (7,588,093/143,477,487) in women (data not shown in tables).

Because the target population for this study is glucocorticoid users, important characteristics are compared in long-term glucocorticoid tablet (LTGS) users, who reported use of glucocorticoid tablets at a cumulative quantity of more than 90 days, and high-risk glucocorticoid (HRGS) users, who reported use of glucocorticoid tablets at a minimal cumulative dose of 450mg prednisone (or its equivalent). Of all glucocorticoid tablet users, 49.6% (6,280,061/12,663,459) are LTGS users and 37.6% (4,754,998/12,663,459) are HRGS users. Of male glucocorticoid tablet users, 47.7% (2,421,374/5,075,366) are LTGS users and 37.4% (1,896,290/5,075,366) are HRGS users. Of female glucocorticoid tablet users, 50.9% (3,858,687/7,588,093) are LTGS users, and 37.7% (2,858,707/7,588,093) are HRGS users. Table 4.1.2 and Table 4.1.3

show the number, average age, average cumulative quantity of glucocorticoid tablets and average glucocorticoid dose per tablet in LTGS users and HRGS users, respectively.

Table 4.1.1 Number and average age of MEPS subjects by gender and year

MEPS	Unweighted				Weighted[§]					
Year	N	%	Ave Age	SD	N	%	Ave Age	SE	95% CI for Mean	
All	272,277									
1996	22,601		33.8	22.1	268,905,492		34.9	0.28	34.4	35.5
1997	34,551		33.8	22.3	271,278,585		35.1	0.25	34.6	35.6
1998	24,072		33.7	22.4	273,533,688		35.3	0.27	34.7	35.8
1999	24,618		34.1	22.3	276,410,763		35.4	0.29	34.8	35.9
2000	25,096		34.2	22.4	278,405,514		35.5	0.29	34.9	36.0
2001	33,556		34.4	22.2	284,247,324		35.9	0.24	35.4	36.3
2002	39,165		34.0	22.2	288,181,764		36.1	0.20	35.7	36.5
2003	34,215		33.5	22.3	290,604,438		36.2	0.21	35.8	36.7
2004	34,403		33.7	22.3	293,526,999		36.3	0.24	35.9	36.8
Ave.	30,253		33.9		280,566,064		35.6	0.16	35.3	36.0
Male	129,916									
1996	10,833	47.9	32.6	21.5	131,526,594	48.9	33.7	0.30	33.1	34.3
1997	16,414	47.5	32.4	21.7	132,605,208	48.9	33.9	0.27	33.4	34.5
1998	11,443	47.5	32.2	21.8	133,614,279	48.8	34.1	0.31	33.5	34.7
1999	11,801	47.9	33.0	22.0	134,602,641	48.7	34.3	0.30	33.7	34.8
2000	12,057	48.0	33.1	22.1	135,881,865	48.8	34.4	0.29	33.8	35.0
2001	16,107	48.0	33.2	21.9	138,630,933	48.8	34.7	0.24	34.3	35.2
2002	18,702	47.8	32.6	21.8	140,801,931	48.9	35.0	0.21	34.6	35.4
2003	16,216	47.4	31.9	21.8	142,264,593	49.0	35.2	0.21	34.7	35.7
2004	16,343	47.5	32.2	21.8	143,869,149	49.0	35.3	0.24	34.8	35.8
Ave.	14,435	47.7	32.6		137,088,576	48.9	34.5	0.16	34.2	34.8
Female	142,361									
1996	11,768	52.1	35.0	22.6	137,378,898	51.1	36.0	0.34	35.4	36.7
1997	18,137	52.5	35.1	22.8	138,673,377	51.1	36.2	0.29	35.6	36.8
1998	12,629	52.5	35.1	22.7	139,919,409	51.2	36.4	0.32	35.8	37.1
1999	12,817	52.1	35.2	22.5	141,808,131	51.3	36.4	0.35	35.7	37.1
2000	13,039	52.0	35.1	22.7	142,523,658	51.2	36.5	0.34	35.8	37.2
2001	17,449	52.0	35.5	22.6	145,616,391	51.2	36.9	0.28	36.4	37.5
2002	20,463	52.2	35.3	22.5	147,379,833	51.1	37.1	0.24	36.6	37.6
2003	17,999	52.6	34.9	22.7	148,339,836	51.0	37.3	0.27	36.7	37.8
2004	18,060	52.5	35.1	22.7	149,657,859	51.0	37.4	0.30	36.8	38.0
Ave.	15,818	52.3	35.1		143,477,487	51.1	36.7	0.18	36.4	37.1

Ave. =average; CI=confidence interval; MEPS=Medical Expenditure Panel Survey; N=number of subjects; SD=standard deviation; SE=standard error of the mean.

[§]Each subject has different year-specific personal weights. .

An estimated 2.2% (6,280,061/280,566,064) of the non-institutional U.S. population are LTGS users; the percentages are 1.8% (2,421,374/137,088,576) in men and 2.7% (3,858,687/143,477,487) in women. The unweighted average number of LTGS users per year in the sample is 607, and the weighted average age is 49.7 years old. Of these LTGS users, 61.4% are female and women are older than men (50.7 versus 48.1 years old; df=1, F=18.66, $p<0.0001$). No significant difference was found in cumulative glucocorticoid dose (df=1, F=1.54, $p=0.2141$) and cumulative quantity of glucocorticoid tablets (df=1, F=0.10, $p=0.7494$) and average glucocorticoid dose per tablet (df=1, F=3.70, $p=0.0545$) between men and women.

An estimated 1.7% (4,754,998/280,566,064) of the non-institutional U.S. population are HRGS users; the percentages are 1.4% (1,896,290/137,088,576) in men and 2.0% (2,858,707/143,477,487) in women. The average unweighted number of HRGS users is 462 per year and the weighted average age is 50.8 years old. Approximately 60.1% of HRGS users are female and women are older than men (52.0 versus 49.2 years old; df=1, F=17.26, $p<0.0001$). No significant difference was found in cumulative glucocorticoid dose (df=1, F=0.14, $p=0.7114$), cumulative quantity of glucocorticoid tablets (df=1, F=1.03, $p=0.3091$) and average glucocorticoid dose (df=1, F=3.00, $p=0.0836$) between female and male HRGS users. Subjects who were classified as both LTGS and HRGS users account for 53.7% of LTGS users and 71.0% of HRGS users (Table 4.1.4).

Table 4.1.2 Number, average age and glucocorticoid tablet use of long-term glucocorticoid tablet users in MEPS by gender and year

LTGS	Unwtd	Weighted[§]							
Gender	N	N	%	Age		Cum. quantity of GS tablets		GS dose per tablet* (mg)	
Year				Ave.	SE	Ave.	SE	Ave.	SE
All	5,461	56,520,549							
1996	464	6,122,964		49.9	1.18	255.3	20.80	10.4	0.46
1997	735	6,190,499		49.0	1.07	268.5	19.10	10.4	0.40
1998	463	5,411,734		48.7	1.23	280.4	30.19	10.3	0.42
1999	457	5,897,846		49.6	4.05	250.2	23.40	11.1	0.35
2000	502	6,546,429		49.7	1.21	225.7	17.40	11.0	0.35
2001	717	6,759,368		50.7	0.87	225.8	15.43	11.1	0.33
2002	854	7,219,940		48.9	0.96	216.0	13.87	11.3	0.30
2003	740	7,237,723		48.1	1.00	205.8	15.71	11.4	0.31
2004	529	5,134,046		52.3	0.92	220.9	17.63	11.4	0.41
Ave.	607	6,280,061		49.7	0.53	237.2	8.93	11.0	0.17
Male	2,064	21,792,370	38.6						
1996	171	2,216,329	36.2	48.2	1.86	285.2	44.16	10.6	0.88
1997	285	2,402,616	38.8	49.8	1.58	274.1	39.04	10.5	0.71
1998	196	2,230,429	41.2	50.0	1.93	277.5	48.52	10.5	0.63
1999	187	2,416,358	41.0	49.0	1.93	248.5	31.92	11.3	0.49
2000	202	2,632,011	40.2	47.1	2.12	228.3	27.89	11.3	0.56
2001	259	2,431,258	36.0	47.6	1.49	237.8	22.45	11.6	0.53
2002	292	2,534,994	35.1	46.3	1.69	213.7	19.16	11.9	0.47
2003	272	2,842,067	39.3	46.4	1.86	195.9	19.71	11.4	0.45
2004	200	2,086,308	40.6	49.6	1.73	207.3	23.74	11.5	0.63
Ave.	229	2,421,374	38.6	48.1	0.90	239.6	14.91	11.2	0.29
Female	3,397	34,728,179	61.4						
1996	293	3,906,635	63.8	50.9	1.37	238.3	23.34	10.2	0.57
1997	450	3,787,883	61.2	48.4	1.22	265.0	22.60	10.3	0.47
1998	267	3,181,305	58.8	47.8	1.37	282.5	37.43	10.2	0.58
1999	270	3,481,489	59.0	50.0	1.30	251.3	31.82	11.0	0.45
2000	300	3,914,418	59.8	51.4	1.53	223.9	21.52	10.8	0.47
2001	458	4,328,110	64.0	52.5	1.00	219.0	19.93	10.7	0.39
2002	562	4,684,946	64.9	50.2	0.98	217.2	16.89	11.0	0.36
2003	468	4,395,656	60.7	50.8	1.03	212.2	20.79	11.5	0.43
2004	329	3,047,739	59.4	54.1	1.04	230.2	23.72	11.3	0.53
Ave.	377	3,858,687	61.4	50.7	0.60	235.7	10.65	10.8	0.19

Ave. =average; Cum. =cumulative; GS=glucocorticoid steroid tablets; LTGS=long-term users of glucocorticoid tablets for at least three months; N=number of subjects; MEPS=Medical Expenditure Panel Survey; SE=standard error of the mean; Unwtd=Unweighted.

[§]Each subject has different year-specific personal weights.

*Doses of various glucocorticoid steroids are converted to prednisone equivalents.

Table 4.1.3 Number, average age and glucocorticoid tablet use of high-risk glucocorticoid tablet users in MEPS by gender and year

HRGS	Unwtd	Weighted[§]							
Gender	N	N	%	Age		Cum. quantity of GS tablets		GS dose per tablet * (mg)	
Year				Ave.	SE	Ave.	SE	Ave.	SE
All	4,162	42,794,978							
1996	351	4,636,824		51.2	1.33	297.8	24.37	11.2	0.55
1997	565	4,735,050		50.0	1.21	292.9	19.74	11.2	0.46
1998	349	3,986,716		49.9	1.44	315.4	33.36	10.9	0.49
1999	366	4,680,070		50.4	1.22	293.5	28.15	11.8	0.40
2000	401	5,217,007		50.7	1.33	268.5	20.75	11.8	0.42
2001	523	4,901,090		52.4	1.01	296.9	20.22	11.9	0.37
2002	639	5,336,783		50.1	1.12	281.3	17.04	11.8	0.33
2003	557	5,342,591		49.9	1.12	267.7	19.35	11.8	0.34
2004	411	3,958,846		53.7	1.03	275.2	21.00	11.9	0.50
Ave.	462	4,754,998		50.8	0.60	286.8	10.34	11.6	0.21
Male	1,612	17,066,606	39.9						
1996	133	1,765,152	38.1	49.4	2.23	308.5	50.59	11.4	1.02
1997	223	1,902,355	40.2	50.0	1.81	275.9	34.45	11.4	0.82
1998	150	1,686,292	42.3	51.2	2.29	290.5	38.00	11.2	0.76
1999	156	2,024,372	43.3	49.6	2.09	286.4	31.01	12.1	0.55
2000	164	2,146,482	41.1	47.7	2.31	267.2	25.30	12.3	0.64
2001	191	1,800,003	36.7	49.7	1.67	307.1	28.92	12.8	0.63
2002	226	1,937,562	36.3	47.6	1.90	270.4	23.33	12.3	0.52
2003	213	2,183,037	40.9	47.1	2.10	246.9	22.67	11.4	0.49
2004	156	1,621,350	41.0	51.2	1.99	256.3	27.19	11.8	0.75
Ave.	179	1,896,290	39.9	49.2	1.11	278.0	14.94	11.9	0.32
Female	2,550	25,728,372	60.1						
1996	218	2,871,672	61.9	52.3	1.69	291.2	28.61	11.1	0.68
1997	342	2,832,696	59.8	50.0	1.41	304.3	25.18	11.0	0.52
1998	199	2,300,424	57.7	48.9	1.71	333.7	48.52	10.7	0.68
1999	210	2,655,698	56.7	51.0	1.61	298.9	31.17	11.7	0.53
2000	237	3,070,525	58.9	52.7	1.68	269.4	26.27	11.5	0.51
2001	332	3,101,087	63.3	53.9	1.21	291.0	27.20	11.5	0.42
2002	413	3,399,220	63.7	51.5	1.09	287.5	21.24	11.6	0.39
2003	344	3,159,554	59.1	51.9	1.19	282.1	26.30	12.0	0.46
2004	255	2,337,496	59.0	55.3	1.16	288.4	28.28	11.9	0.64
Ave.	209	2,858,707	60.1	52.0	0.68	292.7	13.31	11.4	0.23

Ave. =average; Cum. =cumulative; GS=glucocorticoid steroid tablets; HRGS=high-risk users of glucocorticoid tablets at a cumulative prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; N=number of subjects; SE=standard error of the mean; Unwtd=Unweighted.
[§]Each subject has different year-specific personal weights. .
*Doses of various glucocorticoid steroids are converted to prednisone equivalents.

Table 4.1.4 Percentage of subjects classified as LTGS and HRGS users by gender

Subjects Gender	Total LTGS		LTGS & HRGS				Total HRGS	
	Unwtd N	Wtd N	% of LTGS	Unwtd N	Wtd N	% of HRGS	Unwtd N	Wtd N
Male	2,098	21,792,370	53.2	1,120	11,591,271	67.9	1,641	17,066,606
Female	3,454	34,728,179	54.1	1,927	18,774,288	73.0	2,597	25,728,372
Total	5,552	56,520,549	53.7	3,047	30,365,559	71.0	4,238	42,794,978

LTGS=long-term users of glucocorticoid tablets for at least three months; HRGS=high-risk users of glucocorticoid tablets at a cumulative prednisone-equivalent dose of 450 mg or more; N=number of subjects; Unwtd=Unweighted; Wtd=weighted.

4.1.2 Treatment Groups

In addition to glucocorticoid use, study subjects are further classified by type of treatments. Subjects are classified in one of the following groups: the control group (CT) who did not report any anti-osteoporotic agent; the bisphosphonate group (BP) who reported use of bisphosphonate only; the calcitonin group (CN) who reported use of calcitonin only; the HB group who reported use of both hormone replacement therapy and bisphosphonate; the HT group who reported use of hormone replacement therapy only; the raloxifene group (RF) who reported use of raloxifene only; and the OTHER group who reported use of two or more anti-osteoporotic agents, but excluding subjects in the HB group. The ELSE group was used for showing descriptive statistics in this section and is not used for other analyses for this study.

Table 4.1.5 shows the weighted numbers and percentages of subjects who received anti-osteoporotic treatments by gender, type of glucocorticoid use and treatment. It is noted that treatments are reported for both primary and secondary prevention in Table 4.1.5. Overall, 12.0% of MEPS subjects, 22.4% of LTGS users, and 22.8% of HRGS users reported use of any anti-osteoporotic agent. In women, 21.4% of MEPS subjects, 34.8% of LTGS users, and 35.9% of HRGS users reported use

of any anti-osteoporotic agent. In men, only 0.3% of MEPS subjects, 2.5% of LTGS users, and 2.9% of HRGS users reported use of any anti-osteoporotic agent. More women received anti-osteoporotic treatments than men. However, the percentages of glucocorticoid users who received anti-osteoporotic treatments are relatively low. The most frequently used type among all anti-osteoporotic agents is hormone replacement therapy in women or use of both bisphosphonates and calcitonin for men. The next frequently used type is bisphosphonates.

Table 4.1.5 Total weighted number and percentage of subjects by gender, type of glucocorticoid use and treatment, MEPS 1996-2004

GS type	**MEPS**		**LTGS**		**HRGS**	
Treatment*	**Total N[§]**	**%**	**Total N[§]**	**%**	**Total N[§]**	**%**
Women						
BP	13,547,167	1.30	1,199,572	3.42	1,015,601	3.91
CN	2,742,785	0.26	281,275	0.80	281,275	1.08
HB	4,355,743	0.42	395,564	1.13	277,374	1.07
HT	151,153,832	14.53	7,518,676	21.41	5,677,935	21.83
RF	4,583,888	0.44	83,345	0.24	85,345	0.33
ELSE	46,535,244	4.47	2,719,903	7.74	1,991,436	7.66
CT	817,546,517	78.58	22,923,408	65.26	16,676,780	64.13
Total	1,040,465,176	100.00	35,123,743	100.0	26,005,746	100.01[a]
Men						
BP	695,000	0.08	215,809	0.99	170,580	1.00
CN	414,926	0.05	76,222	0.35	76,222	0.45
ELSE	1,401,205	0.17	244,399	1.12	244,399	1.43
CT	838,164,761	99.70	21,255,940	97.54	14,439,076	97.12
Total	840,675,892	100.0	21,792,370	100.00	17,066,606	100.00

GS=glucocorticoid steroids; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group; ELSE=any use of anti-osteoporotic agent(s) other than treatments (BP only, CN only, HB, HT only, RF only) previously identified.

[§]N=total number of subjects from 1996 to 2004.

[a] Sum of percentages does not equal to 100% because of rounding.

Average ages and glucocorticoid use (average cumulative glucocorticoid doses, average cumulative quantities of glucocorticoid tablets and average daily doses per glucocorticoid tablet) were compared across treatment groups. Table 4.1.6 shows the total numbers, average ages, average cumulative quantities of glucocorticoid tablets and average doses per glucocorticoid tablet in subjects with different treatments (data of average cumulative glucocorticoid doses not shown).

- **Age**

Table 4.1.6 shows that average ages are different among treatment groups in female glucocorticoid users (for LTGS users: df=5, F=50.82, $p<0.0001$; for HRGS users: df=5, F=36.78, $p<0.0001$). Post hoc analysis indicated that female glucocorticoid users in the control (CT, both LTGS and HRGS users, $P<0.0001$) and hormone replacement therapy (HT, both LTGS and HRGS users, $P<0.0001$) groups are younger than those in other treatment groups. Similarly, average ages are different among treatment groups in male glucocorticoid users (for LTGS users: df=2, F=7.83, $p=0.0004$; for HRGS users: df=2, F=4.51, $p=0.0112$). Post hoc analysis indicated that male glucocorticoids users in the bisphosphonate (BP) groups are older than those in the control group (both LTGS and HRGS users, $P<0.0001$). Because of significant differences in age among treatment groups, the effect of age on fractures was partially controlled by categorizing study subjects into four age groups (as shown in Tables of Appendix B).

- **Glucocorticoid use**

An overall difference in average cumulative glucocorticoid doses was found among treatment groups in females (for LTGS users: df=5, F=3.70, $p=0.0024$, for

HRGS users: df=5, F=2.32, p=0.0412). Post hoc analysis indicated that female LTGS users in the bisphosphonate (BP) group had a higher average cumulative glucocorticoid dose than those in the HRT (HT, p=0.0364) and control (CT, p=0.0015) groups. Female HRGS users in bisphosphonate groups had a higher average cumulative glucocorticoid dose than those in the calcitonin (CN, p=0.0319) and in the control (CT, p=0.0039) group. Overall differences in average cumulative glucocorticoid doses were found among treatment groups in male glucocorticoid users (for LTGS users: df=2, F=11.80, p<0.0001; for HRGS users: df=2, F=8.46, p=0.0002). Male glucocorticoid users in the bisphosphonate group had higher average cumulative glucocorticoid doses than those in the control (CT, for LTGS users p=0.0030, for HRGS users p=0.0056) groups (results not shown in Table 4.1.6).

Upon further investigation, the cumulative glucocorticoid dose was decomposed to the cumulative quantity of glucocorticoid tablets, which represents the length of glucocorticoid therapy, and the average dose per tablet (results shown in Table 4.1.6). Significant differences in average cumulative quantity of glucocorticoid tablets were found among treatment groups in female glucocorticoid users (for LTGS users: df=5, F=9.72, p<0.0001; for HRGS users: df=5, F=7.87, p<0.0001). Post hoc analysis indicated that female LTGS glucocorticoid users in bisphosphante (BP) group had a longer average period of treatments than those in the HRT (HT, p=0.0364) and the control (CT, p=0.0015) groups. Female LTGS users in the raloxifene group had a shorter average period of treatments than those in the control group (CT, p=0.0138). Female HRGS users in the bisphosphonate group had a longer period of treatments than those in the calcitonin group (CN, p=0.0319). With regard to male glucocorticoid users, significant differences in average cumulative quantity of glucocorticoid tablets were found among treatment groups (for LTGS users: df=2, F=89.94, p<0.0001; for

HRGS users: df=2, F=21.95, $p<0.0001$). Post hoc analysis indicated that male glucocorticoid users in the bisphosphonate (BP) group had longer average periods of treatments than the control groups (for LTGS user: $p=0.0377$; for HRGS users: $p=0.0331$).

Significant differences in average glucocorticoid dose per tablet were found among treatment groups in female LTGS glucocorticoid users (df=5, F=2.89, $p=0.0131$), but not in female HRGS users (df=5, F=2.21, $p=0.0506$). Post hoc analysis indicated that female glucocorticoid users in bisphosphonate (BP) group, control (CT) group and hormone replacement therapy (HT) group had higher average glucocorticoid doses per tablet than those in raloxifene (RF vs. BP $p=0.0093$, CT $p=0.0015$; HT $p=0.0007$) and HB (for BP $p=0.0384$, CT $p=0.0027$, HT $p=0.013$) groups. In male glucocorticoid users, significant differences in average glucocorticoid dose per tablet were found among treatment groups (for LTGS users: df=2, F=3.15, $p=0.0431$; for HRGS users: df=2, F=3.91, $p=0.0203$). Post hoc analysis indicated that subjects in the calcitonin (CN) groups had a lower average glucocorticoid doses per tablet than those in the control groups (both LTGS and HRGS users $p<0.0001$).

Even though an overall statistically significant difference in average glucocorticoid dose per tablet was not found in female HRGS users (df=5, F=2.21, $p=0.0506$), the trends are similar to significant differences found for female LTGS users. It was noted that sample size in the raloxifene groups is relatively small which may not have enough statistical power to detect the differences that may exist. The unweighted sample size of The RF group is 11 and the number was too small to detect the real differences. Based on a personal communication with the staff of MEPS, a sample size of 25 is generally acceptable to yield nationally representative statistics; however, it depends on variance of estimates and also varies by research topics.

Table 4.1.6 Average age and GS use in subjects receiving at least three months of treatment by gender, treatment type and GS type, MEPS 1996-2004

Treatment* / GS type	Unwtd N	Weighted[§] N	Age Ave.	Age SE	Cum. quantity of GS tablets Ave.	Cum. quantity of GS tablets SE	GS dose per tablet**(mg) Ave.	GS dose per tablet**(mg) SE
Female								
BP	1,275	13,547,167	70.1	0.52	336.1	54.07	11.3	0.78
LTGS	125	1,199,572	67.3[a d]	2.53	437.7[a]	64.19	11.1[c e]	0.91
HRGS	111	1,015,601	65.3[a d]	2.86	488.6[a]	73.26	11.0	0.66
CN	236	2,742,785	72.4	0.82	239.5	69.40	8.8	0.21
LTGS	24	281,275	64.7[a d]	2.34	312.8	86.86	8.8	0.09
HRGS	24	281,275	64.7[a d]	2.34	312.8	86.86	8.8	0.09
HB	402	4,355,743	64.7	0.71	205.6	55.89	9.4	0.74
LTGS	42	395,564	61.2[a e]	2.69	318.1	59.68	7.9[a d f]	0.31
HRGS	32	277,374	65.9[a d]	-	433.3	-	9.2	-
HT	13,749	151,153,832	50.8	0.28	140.8	17.46	10.7	0.32
LTGS	699	7,518,676	55.6[a b e f]	0.76	237.4	30.84	11.4[c e]	0.48
HRGS	523	5,677,935	57.0[a b c e f]	0.81	303.5	38.54	11.9	0.56
RF	419	4,583,888	65.7	0.64	152.7	85.20	7.2	0.21
LTGS	11	85,345	74.1[a c d]	-	609.5	-	6.9[a d f]	-
HRGS	11	85,345	74.1[a d]	-	609.5	-	6.9	-
CT	85,810	817,546,517	35.6	0.20	112.8	6.06	10.7	0.19
LTGS	2,269	22,923,408	47.2[b c d e f]	0.74	208.4[f]	10.84	10.8[c e]	0.24
HRGS	1,682	16,676,780	48.4[b c d e f]	0.88	255.6[f]	14.00	11.5	0.28
Male								
BP	67	695,000	65.0	0.01	1,120.9	-	8.2	-
LTGS	26	215,809	67.1[a]	-	1,390.9[a]	-	8.4	-
HRGS	22	170,580	64.7[a]	-	870.7[a]	-	8.6	-
CN	40	414,926	77.2	1.11	545.7	255.01	8.2	0.62
LTGS	10	76,222	61.8	6.26	668.0	343.75	5.4[a]	0.11
HRGS	10	76,222	61.8	6.26	668.0	343.75	5.4[a]	0.11
CT	81.287	838,164,761	37.0	0.20	113.5	6.28	10.9	0.20
LTGS	2,003	21255,940	47.7[f]	0.91	213.6[f]	11.53	11.3[b]	0.29
HRGS	1,555	16,575,405	48.7[f]	1.12	254.4[f]	12.73	12.0[b]	0.32

Ave. =average; Cum. =cumulative; GS=glucocorticoid steroid tablets; GS doses of various glucocorticoid steroids are converted to as prednisone equivalents; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. SE=standard error of the mean; Unwtd=unweighted

[§]Each subject has different year-specific personal weights. .

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group;

**Doses of various glucocorticoid steroids are converted to prednisone equivalents.

[a] $p<0.05$ compared to CT; [b] $p<0.05$ compared to CN; [c] $p<0.05$ compared to HB; [d] $p<0.05$ compared to HT; [e] $p<0.05$ compared to RF, [f] $p<0.05$ compared to BP.

- **Summary of Results for Study Objective One**

There was no significant difference in average cumulative glucocorticoid doses among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments, so hypothesis Ho_{1B3} was not rejected. However, all other hypotheses for the first study objective were rejected because statistically significant differences were found in average ages and glucocorticoid use among different treatment groups. These differences are briefly summarized as follows.

Female groups are older than male groups regardless of glucocorticoid use. Female glucocorticoid users in the hormone replacement threpay (HT) and the control (CT) groups were younger than those in other treatment groups. Compared to male glucocorticoid users in the calcitonin (CN) group, those in the control (CT) group are younger and those in the bisphosphonate (BP) group are older. The effect of age on fracture rates was partially controlled by dividing subjects into four age groups, which are 11-30, 31-50, 51-70 and 71-90 years old..

Female glucocorticoid users in the bisphosphonate (BP) group, hormone replacement therapy (HT) and the control (CT) groups had significantly higher average glucocorticoid doses per tablet than those in other groups, but those in the HT and CT groups are younger than those in other group. The overall impact of glucocorticoid use and age on fracture rates for female glucocorticoid users in the HT and CT groups were unclear. However, it is likely that more glucocorticoid use in female glucocorticoid users of the bisphosphonate (BP) and raloxifene (RF) groups will have a negative impact on osteoporotic fractures. Similarly, male glucocorticoid users in the control group had higher average glucocorticoid doses per tablet and are younger than the bisphosphonate and the control groups. The overall impact of glucocorticoid use and

age on fracture rates for male glucocorticoid users in the CT groups were unclear. These findings suggested a selection bias. Readers should be aware of these differences when interpreting economic and clinical outcomes among different treatment groups throughout this chapter.

4.1.3 Race Groups

In MEPS data from 1996 to 2004, 81.7% of subjects are white, 12.8% are black or African American, 4.0% are Asian, Hawaiian or Pacific Islanders, 0.9% are American Indian or Alaska Native, and 0.6% reported no race or multiple race groups or other type of race group. The majority of glucocorticoid users (86.2% of LTGS and 86.3% of HRGS) are white, followed by black (10.0% of LTGS and 10.3% of HRGS) and Asian or Pacific Islanders (2.4% of LTGS and 2.4% of HRGS). Table 4.1.7 shows national estimates of percentages of subjects by race group.

Table 4.1.7 Weighted Percentages of subjects by racial group and glucocorticoid type

GS type	MEPS			LTGS			HRGS		
Racial group (%)	**All**	**Male**	**Female**	**All**	**Male**	**Female**	**All**	**Male**	**Female**
White	81.67	82.29	81.08	86.21	86.98	85.72	86.26	87.37	85.53
Black	12.84	12.26	13.39	10.02	9.39	10.41	10.29	9.22	11.00
Asian / Pacific Islander	4.03	4.02	4.05	2.42	2.16	2.58	2.44	2.34	2.52
American Indian / Alaska Native	0.91	0.91	0.90	0.85	0.99	0.77	0.69	0.80	0.63
Other	0.55	0.52	0.58	0.51	0.49	0.51	0.31	0.28	0.33
Total	100.00	100.00	100.00	100.01[a]	100.01[a]	99.99[a]	99.99[a]	100.01[a]	100.01[a]

HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey.

[a] Sum of percentages does not equal to 100% because of rounding.

Next, percentages of subjects in racial groups within each type of treatment are listed in Table 4.1.8 and Table 4.1.9. Approximately 90% of female glucocorticoid users in the BP, CN, HB or HT groups are white. Almost all male subjects who received anti-osteoporotic therapy are white. Among female subjects in the same racial group, hormone replacement therapy (HT) was most frequently used anti-osteoporotic treatment; it is followed by bisphosphonate treatments except for MEPS female subjects in the American Indian/Alaska Native group. More bisphosphonates were used in male subjects of the same racial group, except MEPS male subjects in the American Indian/ Alaska Native group.

In each racial group, the majority of women received hormone replacement therapy (HT) for management of osteoporosis (Table 4.1.8). The next most popular anti-osteoporotic treatment was bisphosphonates within most racial groups. It is noted that the unweighted number of female glucocorticoid users in the RF group is 11, that fewer than 30 male glucocorticoid users were identified in the BP group, and that there were 10 male glucocorticoid users in the CN group, so these percentages in race groups may not be representative.

Table 4.1.8 Weighted percentages of female subjects by treatment and racial group

Treatment*	BP	CN	HB	HT	RF	CT	
Racial group	Col. % Row %	Col. % Row %	Col. % Row %	Col. % Row %	Col. % Row %	Col. % Row %	Total row %†
MEPS							
White	92.69	96.49	94.49	90.28	91.94	81.54	
	7.85	**1.65**	**2.57**	**85.29**	**2.63**	**-**	**100.01** [a]
Black	4.47	2.21	1.77	6.58	3.02	13.44	
	5.60	**0.56**	**0.71**	**91.85**	**1.28**	**-**	**100.00**
Asian/Pacific Islander	2.53	0.86	2.80	1.86	3.10	3.55	
	9.97	**0.69**	**3.54**	**81.67**	**4.13**	**-**	**100.00**
American Indian/	0.15	0	0.51	0.83	0.28	0.89	
Alaska Native	**1.55**	**0**	**1.69**	**95.78**	**0.99**	**-**	**100.01** [a]
Other	0.15	0.44	0.44	0.45	1.66	0.57	
	2.54	**1.47**	**2.34**	**84.32**	**9.33**	**-**	**100.00**
Total column %	99.99 [a]	100.00	100.01 [a]	100.00	100.00	99.99 [a]	
LTGS							
White	90.49	100.0	94.65	90.93	77.59	82.84	
	12.56	**3.25**	**4.33**	**79.09**	**0.77**	**-**	**100.00**
Black	7.81	0	0	5.06	22.41	13.33	
	19.00	**0**	**0**	**77.12**	**3.88**	**-**	**100.00**
Asian/Pacific Islander	0	0	5.35	2.14	0	2.81	
	0	**0**	**11.60**	**86.40**	**0**	**-**	**100.00**
American Indian/	1.70	0	0	1.58	0	0.47	
Alaska Native	**14.60**	**0**	**0**	**85.40**	**0**	**-**	**100.00**
Other	0	0	0	0.29	0	0.54	
	0	**0**	**0**	**100.00**	**0**	**-**	**100.00**
Total column %	100.00	100.00	100.00	100.00	100.00	99.99 [a]	
HRGS							
White	88.77	100.0	100.0	90.60	77.59	82.51	
	13.52	**4.22**	**4.16**	**77.12**	**0.99**	**-**	**100.01** [a]
Black	9.23	0	0	5.39	22.41	14.15	
	22.36	**0**	**0**	**73.07**	**4.56**	**-**	**99.99** [a]
Asian/Pacific Islander	0	0	0	2.44	0	2.64	
	0	**0**	**0**	**100.00**	**0**	**-**	**100.00**
American Indian/	2.00	0	0	1.57	0	0.23	
Alaska Native	**18.62**	**0**	**0**	**81.38**	**0**	**-**	**100.00**
Other	0	0	0	0	0	0.47	
	0	**0**	**0**	**0**	**0**	**-**	**0**
Total column %	100.00	100.00	100.00	100.00	100.00	100.00	

HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey.
† not included The CT group.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
[a] Sum of percentages does not equal to 100% because of rounding.

Table 4.1.9 Weighted percentages of male subjects by treatment and racial group

Treatment*	BP	CN	CT	
Racial group	Col. % Row %	Col. % Row %	Col. % Row %	Total row %†
MEPS				
White	99.18	96.41	84.93	
	63.28	**36.72**	-	**100.00**
Black	0	0	10.35	
	0	**0**	-	**0**
Asian/Pacific	0	0	3.32	
Islander	**0**	**0**	-	**0**
American Indian/	0	3.59	0.87	
Alaska Native	**0**	**100.00**	-	**100.00**
Other	0.82	0	0.53	
	100.00	**0**	-	**100.00**
Total column %	100.00	100.00	100.00	
LTGS				
White	100.0	100.0	86.74	
	73.90	**26.10**	-	**100.00**
Black	0	0	9.62	
	0	**0**	-	**0**
Asian/Pacific	0	0	2.12	
Islander	**0**	**0**	-	**0**
American Indian/	0	0	1.01	
Alaska Native	**0**	**0**	-	**0**
Other	0	0	0.50	
	0	**0**	-	**0**
Total column %	100.00	100.00	99.99 [a]	
HRGS				
White	100.00	100.00	87.11	
	69.12	**30.88**	-	**100.00**
Black	0	0	9.49	
	0	**0**	-	**0**
Asian/Pacific	0	0	2.29	
Islander	**0**	**0**	-	**0**
American Indian	0	0	0.82	
/Alaska Native	**0**	**0**	-	**0**
Other	0	0	0.28	
	0	**0**	-	**0**
Total column %	100.00	100.00	99.99 [a]	

HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey.

† not included The CT group.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

[a] Sum of percentages does not equal to 100% because of rounding.

4.1.4 Underlying Conditions

Another important factor, which may have an impact on fracture rates, is the underlying disease for which glucocorticoid steroids were used. Table 4.1.10 lists some common conditions in MEPS subjects, LTGS or HRGS users identified by International Classification of Disease, the ninth edition, Clinical Modification (ICD-9-CM) codes and Clinical Classification Code (CCC) codes. Based on the list, at least 25.3% of LTGS users reported respiratory diseases, including asthma (CCC=128), chronic obstructive pulmonary diseases (CCC=127), lower and upper respiratory problems (CCC=126, 133, 134), followed by joint problems (21.9%), including non-traumatic joint disorders (CCC=204), rheumatoid arthritis (CCC=202) and connective tissue diseases (CCC=211). By following the same calculation, approximately 24.1% of HRGS users reported respiratory diseases, and 23.3% reported joint problems. The percentages of conditions for LTGS and HRGS users are similar.

When LTGS users are categorized by type of anti-osteoporotic treatments, percentages of some conditions are listed in Table 4.1.11. Joint problems remain the top ranked underlying condition, followed by respiratory diseases in LTGS users with most types of anti-osteoporotic treatments. Table 4.1.11 does not indicate a potential difference in preference of anti-osteoporotic treatments in LTGS users with the same condition. This issue is beyond the scope of this study and, furthermore, the sample size in some treatment groups is too small to have sufficient statistical power to draw any conclusion.

Table 4.1.10 Percentages of selected conditions for which glucocorticoid steroids were prescribed by glucocorticoid type, MEPS 1996-2004

Code	Condition	Unwtd %		
		GS	LTGS	HRGS
ICD-9-CM[§]				
493	Asthma	11.60	12.85	12.68
716	Arthropathies, nec	5.88	9.35	10.17
714	Rheumatoid arthritis/ inflammatory polyarthropathies	4.89	8.01	8.51
710	Diffuse diseases of connective tissue	2.34	3.74	4.06
492	Emphysema	2.26	3.55	3.84
692	Contact dermatitis	6.92	2.98	2.57
725	Polymyalgia rheumatica	1.23	2.10	2.19
255	Adrenal gland disorders	1.00	1.62	1.80
555	Regional enteritis	0.99	1.34	1.73
496	Chronic airway obstruction, nec	0.89	1.42	1.36
401	Essential hypertension	1.57	1.22	1.31
782	Skin and other integument symptoms	4.84	1.70	1.30
518	Other lung diseases	0.73	1.12	1.18
135	Sarcoidosis	0.63	1.09	1.18
490	Bronchitis, nos	1.98	1.40	1.16
477	Allergic rhinitis	2.08	1.39	0.99
696	Psoriasis/like disorders	1.19	0.78	0.76
473	Chronic sinusitis	1.12	1.02	0.58
CCC[§]				
128	Asthma	11.60	12.85	12.68
204	Other non-traumatic joint disorders	6.46	10.04	10.88
202	Rheumatoid arthritis and related disorders	4.97	8.09	8.61
127	Chronic obstructive pulmonary diseases	5.29	6.56	6.49
210	Systemic lupus erythematosus and conditions	2.34	3.74	4.06
211	Other connective tissue diseases	2.73	3.74	3.78
253	Allergic reactions	8.30	3.74	3.23
133	Other lower respiratory disorders	2.24	2.67	2.66
144	Regional enteritis and ulcerative colitis	1.44	2.20	2.38
051	Other endocrine disorders	1.49	2.19	2.23
200	Other skin disorders	6.73	2.19	1.74
134	Other upper respiratory diseases	2.53	1.65	1.18
126	Other upper respiratory infections	2.71	1.61	1.05

GS=glucocorticoid steroid tablets; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; nec=not elsewhere classified; nos=not specified as acute or chronic, Unwtd=unweighted.

[§]ICD-9-CM=International Classification of Disease, the ninth edition, Clinical Modification, CCC=Clinical Classification Code.

Table 4.1.11 Percentages of selected conditions for which glucocorticoid steroids were prescribed by type of treatment, MEPS 1996-2004

Code	Condition	Treatment* (% unwtd LTGS users)						
		Male		Female				
		BP	CN	BP	CN	HB	HT	RF
ICD-9-CM[§]								
493	Asthma	4.88		4.83			10.05	
716	Arthropathies, nec	22.76		11.98	13.92	18.13	12.30	50.70
714	Rheumatoid arthritis/ inflammatory polyarthropathies	25.20	10.53	15.64	30.38	27.50	8.98	
710	Diffuse diseases of connective tissue			4.16	7.59	7.50	5.03	
492	Emphysema	13.82		3.99			1.02	
692	Contact dermatitis				2.53	1.25	2.14	
725	Polymyalgia rheumatica			5.32			2.35	
255	Adrenal gland disorders						2.78	
555	Regional enteritis		21.05	2.66			1.28	
496	Chronic airway obstruction, nec			0.33	10.13		0.80	
401	Essential hypertension			0.50			0.59	4.00
518	Other lung diseases	12.20		0.17	10.13	1.25	1.55	
135	Sarcoidosis		8.77	3.83			0.80	
490	Bronchitis, nos			1.16	2.53		1.18	
477	Allergic rhinitis	4.07			5.06	2.50	1.50	1.33
696	Psoriasis/like disorders					6.88	1.07	
473	Chronic sinusitis					4.38	2.51	
CCC[§]								
128	Asthma	4.88		4.83			10.05	
204	Other non-traumatic joint disorders	22.76		12.48	13.92	18.13	13.58	50.70
202	Rheumatoid arthritis & related disorders	34.96	10.53	15.64	30.38	27.50	8.98	
127	Chronic obstructive pulmonary diseases	14.63		5.82	12.66	1.88	3.42	
210	Systemic lupus erythematosus			4.16	7.59	7.50	5.03	
211	Other connective tissue diseases	0.81		5.32			3.80	17.30
253	Allergic reactions			1.16	2.53	1.25	2.99	
133	Other lower respiratory disorders	12.20		0.50	10.13	3.75	3.21	
144	Regional enteritis and ulcerative colitis		21.05	2.66			1.28	
051	Other endocrine disorders			0.17		5.63	4.01	
200	Other skin disorders			3.00			2.41	
134	Other upper respiratory diseases	4.07			5.06	2.50	1.66	1.33
126	Other upper respiratory infections			0.17	2.53	4.38	3.32	

LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; nec=not elsewhere classified; nos=not specified as acute or chronic; Unwtd=unweighted.
[§]ICD-9-CM=International Classification of Disease, the ninth edition, Clinical Modification, CCC=Clinical Classification Code.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

4.2 CLINICAL OUTCOMES

This section describes national estimates of prevalence and incidence rates for glucocorticoid-induced osteoporosis and glucocorticoid-induced osteoporotic fractures in the U.S. These estimates are obtained from the cross-sectional analyses of MEPS data from 1996 to 2004. Prevalence rates are calculated regardless of the start date of anti-osteoporotic treatment. To better estimate the causal relations between incidence of osteoporosis (or osteoporotic fractures) and use of anti-osteoporotic agents, incidences which were reported 90 days after the initiation of anti-osteoporotic therapy (the index date) are included in calculations for incidence rates. The results from this section address the second study objective.

4.2.1 Prevalence

National estimates of average annual prevalence rates of osteoporosis and osteoporotic fractures in the U.S. from 1996 to 2004 are summarized in Table 4.2.1 by gender and age groups. It is noted that the number of male LTGS users, for example, is larger than the sum of male LTGS users in four age groups; this can be explained by two reasons. First, subjects younger than 11 or older than 90 years of age are not included in the four age groups, but are included in the total number of subjects. Second, subjects with invalid age values (including missing) were not included in the calculation within age groups.

Table 4.2.1 Average annual prevalence of osteoporosis and osteoporotic fractures in subjects by glucocorticoid type and age group, MEPS 1996-2004

Subject*	N[§]		Osteoporosis			Osteoporotic fractures		
Age	**Unwtd**	**Wtd**	**Unwtd**	**Wtd**	**P (/10^6)**	**Unwtd**	**Wtd**	**P(/10^6)**
MEPS	183,333	1,833,687,259	2,344	24,595,274	13,413	3,091	33,410,396	18,220
Male	81,442	839,757,327	142	1,381,956	1,646	1,416	15,525,076	18,488
11-30	18,844	194,850,218	4	5,209	27	319	3,571,355	18,329
31-50	21,954	242,561,578	17	147,636	609	426	4,704,402	19,395
51-70	16,511	175,489,396	60	605,396	3,450	282	2,906,371	16,562
71-90	7,071	75,801,560	60	567,963	7,493	186	2,233,042	29,459
Female	101,891	993,929,932	2,202	23,213,318	23,355	1,675	17,885,320	17,995
11-30	24,899	244,530,244	9	73,910	302	230	2,555,949	10,452
31-50	30,562	303,822,624	159	1,350,446	4,445	367	3,844,127	12,653
51-70	2,022	197,491,690	1,014	10,391,432	52,617	369	3,645,001	18,456
71-90	10,499	106,602,271	990	11,006,812	103,251	568	6,305,504	59,150
LTGS	5,209	53,951,811	237	2,400,065	44,485	146	1,612,532	29,888
Male	2,039	21,547,971	23	210,478	9,768	52	641,347	29,764
11-30	336	3,340,638	0	0	0	5	41,649	12,467
31-50	470	5,270,509	6	38,173	7,243	12	163,371	30,997
51-70	622	6,444,968	9	73,374	11,385	21	265,465	41,189
71-90	365	4,116,138	8	98,930	24,035	11	122,831	29,841
Female	3,170	32,403,840	214	2,189,587	67,572	94	971,185	29,971
11-30	363	3,752,320	4	22,213	5,920	4	56,953	15,178
31-50	1,038	11,106,726	25	206,954	18,633	23	203,340	18,308
51-70	1,051	10,445,885	84	881,200	84,359	25	217,418	20,814
71-90	547	5,464,289	93	982,412	179,788	35	398,558	72,939
HRGS	3,970	40,836,518	204	1,998,212	48,932	118	1,295,881	31,733
Male	1,587	16,822,207	19	155,297	9,232	43	552,088	32,819
11-30	251	2,567,643	0	0	0	4	31,412	12,234
31-50	368	4,059,678	4	17,615	4,339	8	131,442	32,377
51-70	492	5,085,343	9	73,374	14,429	18	235,405	46,291
71-90	297	3,365,873	6	64,308	19,106	11	122,831	36,493
Female	2,383	24,014,311	185	1,842,915	76,742	75	743,793	30,973
11-30	253	2,582,540	4	22,213	8,601	2	31,354	12,141
31-50	737	7,768,111	20	161,816	20,831	16	116,166	14,954
51-70	805	7,919,931	77	766,169	96,739	21	179,008	22,602
71-90	463	4,541,641	78	820,044	180,561	30	326,826	71,962

HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. Wtd=weighted; Unwtd=Unweighted.

*Total number of subjects includes those records with the missing value of age, so may be larger than sum of subjects in age groups.

[§]N=total number of subjects from 1996 to 2004.

P=prevalence per 1,000,000 person-years.

Gender is another factor; women generally have higher prevalence rates of osteoporosis than men in groups of the same range of age. Glucocorticoid use also plays an important role. Glucocorticoid users have higher prevalence rates of osteoporosis than overall MEPS subjects within the same range of age and same gender. The prevalence rates of osteoporotic fractures between LTGS and HRGS users are similar within the same range of age and same gender.

For most cases, prevalence rates of osteoporosis and osteoporotic fractures increase with increased age. Prevalence rates of osteoporosis and osteoporotic fractures for subjects aged 50 years old or older are reported as follows. Overall, the prevalence rate of osteoporosis and osteoporotic fractures in MEPS subjects aged 50 years old or older for this study are $40{,}641/10^6$ person-years (22,571,603/555,384,917) and $27{,}170/10^6$ person-years (15,089,918/555,384,917), respectively. In all men aged 50 years old and over, the average annual prevalence rates are $4{,}669/10^6$ person-years for osteoporosis and $20{,}452/10^6$ person-years for osteoporotic fracture. In all women aged 50 years old and over, the average annual prevalence rates are $70{,}367/10^6$ person-years for osteoporosis and $32{,}722/10^6$ person-years for osteoporotic fracture.

Overall, the prevalence rate of osteoporosis and osteoporotic fractures in LTGS users aged 50 years old or older for this study are $76{,}910/10^6$ person-years and $37{,}938/10^6$ person-year, respectively. In male LTGS users aged 50 years old and over, the average annual prevalence rates are $16{,}315/10^6$ person-years for osteoporosis and $36{,}767/10^6$ person-years for osteoporotic fracture. In female LTGS users aged 50 years old and over, the average annual prevalence rates are $117{,}133/10^6$ person-years for osteoporosis and $38{,}716/10^6$ person-years for osteoporotic fracture.

Overall, the prevalence rates of osteoporosis and osteoporotic fractures in HRGS users aged 50 years old or older for this study are $82{,}433/10^6$ person-years and $41{,}318/10^6$

person-year, respectively. In male HRGS users aged 50 years old and over, the average annual prevalence rates are $16{,}291/10^6$ person-years for osteoporosis and $42{,}389/10^6$ person-years for osteoporotic fracture. Finally, in female HRGS users aged 50 years old and over, the average annual prevalence rates are $127{,}288/10^6$ person-years for osteoporosis and $40{,}592/10^6$ person-years for osteoporotic fracture.

4.2.2 Incidence Rates of Osteoporosis

The incidence of osteoporosis (or osteoporotic fractures) for a subject is an episode reported by the control group during the data collection period of MEPS or a new episode reported by subjects receiving an anti-osteoporotic agent after 90 days of initiation of therapy. Incidence rates are often different among subjects with different experiences in prior exposure to osteoporosis and/or osteoporotic fractures; therefore, these rates are summarized and reported in groups based on different prior exposure. A prior exposure in osteoporosis (or osteoporotic fractures) is defined for this study when a subject had an episode of osteoporosis or osteoporotic fractures before the index date of anti-osteoporotic treatment or within 90 days of initiation of therapy. Furthermore, these rates were used in Markov modeling in Section 4.4. Therefore, subjects are classified into one of the following three states: the WELL, GIOP or GIFX state. Subjects without prior osteoporosis and osteoporotic fractures are grouped in the WELL state; those with prior osteoporosis without any prior osteoporotic fracture are in the; and those with prior osteoporotic fracture(s) are in the GIFX state. Table 4.2.2 shows the weighted number and percentage of subjects in each state.

Table 4.2.3 shows incidence rates of osteoporosis for women in the WELL state. Glucocorticoid users in the CN and HB groups have relatively higher incidence rates of

osteoporosis than those in other treatment groups. In addition to protective effects from the treatment, a possible explanation is that the sample size in the CN and HB groups may be too small to reach the statistical power needed to detect osteoporosis. On the other side, subjects in the control (CT) and hormone replacement therapy (HT) groups have relatively lower incidence rates of osteoporosis than those in other groups (chi-square test, $p<0.0001$).

In general, incidence rates of osteoporosis in female glucocorticoid tablet users are higher than those rates in MEPS female subjects, except for subjects in bisphosphonate and raloxifene groups. The rates between LTGS and HRGS users are similar. This phenomenon may indicate the negative effect of glucocorticoid use on incidence of osteoporosis, and that glucocorticoid use for over three months or high cumulative glucocorticoid dose may have a similar effect on incidence of osteoporosis.

However, BP users of the MEPS group have a relatively higher incidence rate than those with glucocorticoid use. One possible explanation for this phenomenon is selection bias. It has been discussed in the literature that osteoporosis and vertebral fractures are often under-diagnosed. Increasing the chance of screening may increase the probability of early detection of osteoporosis and osteoporotic fractures. Subjects in some treatment groups, for example, the BP and HB groups, may be proactive to screening which increases the probability of detecting a new incidence of osteoporosis. Additionally, the younger average age of glucocorticoid users in the BP group than those of MEPS may be another factor (see Table 4.1.6).

Table 4.2.2 Weighted number and percentage of subjects in each state by gender and treatment group, MEPS 1996-2004

State	Weighted						
	WELL		GIOP		GIFX		
*Treatment**	N[§]	%	N[§]	%	N[§]	%	Total[§]
Women							
MEPS							
BP	7,547,768	55.05	5,402,484	39.41	759,690	5.54	13,709,942
CN	1,328,204	48.12	1,097,498	39.76	334,481	12.12	2,760,183
HB	2,577,252	58.75	1,680,494	38.31	129,162	2.94	4,386,908
HT	149,478,066	98.79	1,185,942	0.78	638,454	0.42	151,302,462
RF	3,839,675	83.76	678,515	14.80	65,699	1.43	4,583,889
CT	817,546,517	97.83	5,363,149	0.64	12,806,558	1.53	835,716,224
LTGS							
BP	573,947	47.85	492,065	41.02	133,560	11.13	1,199,572
CN	162,800	57.88	72,069	25.62	46,406	16.50	281,275
HB	286,900	72.53	101,944	25.77	6,719	1.70	395,563
HT	7,291,654	96.78	216,683	2.88	26,143	0.35	7,534,480
RF	47,065	55.15	38,280	44.85	0	0	85,345
CT	22,923,408	95.09	570,481	2.37	613,730	2.55	24,107,619
HRGS							
BP	504,664	49.69	409,344	40.31	101,593	10.00	1,015,601
CN	162,800	57.88	72,069	25.62	46,406	16.50	281,275
HB	239,512	86.35	31,143	11.23	6,719	2.42	277,374
HT	5,474,244	96.41	193,353	3.41	10,338	0.18	5,677,935
RF	47,065	55.15	38,280	44.85	0	0	85,345
CT	16,676,780	94.66	501,987	2.85	439,593	2.50	17,618,360
Men							
MEPS							
BP	449,008	63.69	232,678	33.00	23,320	3.31	705,006
CN	248,773	59.96	83,718	20.18	82,435	19.87	414,926
CT	838,164,761	98.10	818,787	0.10	15,399,002	1.80	854,382,550
LTGS							
BP	124,087	57.50	91,723	42.50	0	0	215,810
CN	64,842	85.07	11,380	14.93	0	0	76,222
CT	21,255,940	96.81	67,977	0.31	631,608	2.88	21,955,525
HRGS							
BP	113,480	66.53	57,101	33.47	0	0	170,581
CN	64,842	85.07	11,380	14.93	0	0	76,222
CT	16,575,405	96.56	47,419	0.28	542,349	3.16	17,165,173

WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures; MEPS=Medical Expenditure Panel Survey.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group;

[§] N=total number of subjects from 1996 to 2004.

Table 4.2.3 Incidence of osteoporosis in women without prior osteoporosis and fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Female	WELL state		Osteoporosis			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS female	100,818	982,317,482	1,224	12,538,043		12,764	
BP	722	7,547,768	246	2,535,696	71.5	335,953	97,287
CN	122	1,328,204	30	349,905	70.8	263,442	73,593
HB	245	2,577,252	74	763,565	68.3	296,271	84,093
HT	13,575	149,478,066	254	2,769,737	64.4	18,529	4,665
RF	344	3,839,675	66	755,991	66.3	196,889	53,340
CT	85,810	817,546,517	554	5,363,149	69.0	6,560	1,644
LTGS female	3,064	31,285,774	116	1,128,856		36,082	
BP	69	573,947	21	153,306	61.8	267,108	74,748
CN	16	162,800	8	89,179	58.6	547,783	179,957
HB	32	286,900	14	113,925	75.5	397,090	118,823
HT	671	7,291,654	17	201,965	67.0	27,698	6,998
RF	7	47,065	0	-	-	-	-
CT	2,269	22,923,408	56	570,481	67.7	24,886	6,281
HRGS female	2,293	23,105,065	101	959,036		41,508	
BP	63	504,664	19	135,388	61.0	268,274	75,116
CN	16	162,800	8	89,179	58.6	547,783	179,957
HB	26	239,512	14	113,925	75.5	475,655	149,049
HT	499	5,474,244	11	118,557	70.1	21,657	5,459
RF	7	47,065	0	-	-	-	-
CT	1,682	16,676,780	49	501,987	66.5	30,101	7,612

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; WELL state: subjects without any prior osteoporosis and osteoporotic fractures; Wtd=weighted; Unwtd=unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group;

**Rates per 1,000,000 person-years.

Table 4.2.4 shows the incidence rates of osteoporosis in men. The issue of lack of statistical power due to small sample size is observed. The information provided in Table 4.2.4 is insufficient to draw any conclusion.

Table 4.2.4 Incidence of osteoporosis in men without prior osteoporosis and fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Male	**WELL state**		**Osteoporosis**			**Incidence (/10^6)****	
GS type Treatment*	**Unwtd N§**	**Wtd. N§**	**Unwtd N§**	**Wtd. N§**	**Ave. Age**	**1-year rate**	**3-month rate**
MEPS male	81,359	838,862,542	109	1,032,044		1,230	
BP	44	449,008	17	195,496	65.0	435,395	133,166
CN	28	248,773	2	17,761	90.0	71,394	18,347
CT	81,287	838,164,761	90	818,787	63.2	977	244
LTGS male	2,029	21,444,869	13	107,375		5,007	
BP	18	124,087	6	39,398	63.7	317,503	91,081
CN	8	64,842	0	-	-	-	-
CT	2,003	21,255,940	7	67,977	59.0	3,198	800
HRGS male	1,579	16,753,727	11	86,817		5,182	
BP	16	113,480	6	39,398	63.7	347,180	101,127
CN	8	64,842	0	-	-	-	-
CT	1,555	16,575,405	5	47,419	64.4	2,861	716

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; WELL state: subjects without any prior osteoporosis and osteoporotic fractures; Wtd=weighted; Unwtd=Unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

4.2.3 Incidence Rates of Osteoporotic Fractures

Table 4.2.5 to Table 4.2.10 show incidence rates of osteoporotic fractures in women and men with different prior exposure to osteoporosis and osteoporotic fractures. It is estimated that the overall annual incidence rates of osteoporotic fractures are 16,306 per 10^6 person-years (PY) (29,866,357/1,831,575,101) for all MEPS subjects, 17,175 per

10^6 PY (14,413,308/839,212,686) for male MEPS subjects, and 15,572 per 10^6 PY (15,453,049/992,362,415) for female MEPS subjects. The estimated annual incidence rates of osteoporotic fractures in LTGS users are 24,116 per 10^6 PY for all LTGS users, 27,199 per 10^6 PY for male LTGS users and 22,054 per 10^6 PY for female LTGS users. In HRGS users, the estimated annual incidence rates of osteoporotic fractures are 26,543 per 10^6 PY for all HRGS users, 32,063 per 10^6 PY for male HRGS users and 22,649 per 10^6 PY for female HRGS users.

The use of glucocorticoid steroids increases the incidence of osteoporotic fractures. Overall, higher annual incidence rates of osteoporotic fractures increase are observed when comparing rates in glucocorticoid users to those in all MEPS subjects. Annual incidence rates of osteoporotic fractures in HRGS users are slightly higher than those in LTGS users, but they are close.

Compared to subjects in the WELL state, those in the GIFX state have the highest incidence rates of osteoporotic fractures within the same treatment, followed by those in the GIOP state. The effect of glucocorticoid use on the incidence of osteoporotic fractures is unclear. The effects of anti-osteoporotic treatments on the incidence rates of osteoporotic fractures are inconclusive because of limited information in the tables.

No incidence of osteoporotic fractures was observed in some cases in these tables. Possible explanations are that treatments may reduce the risks of osteoporotic fractures, and that the period of data collection for a MEPS subject is two years which may be too short to detect all osteoporotic fractures. Another probable explanation, as described earlier, is that a small sample size may not have enough statistical power to detect incidence of osteoporotic fractures.

Table 4.2.5 Incidence of first osteoporotic fracture in women without prior osteoporosis and fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Female	WELL state		1st Fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS female	100,264	976,954,333	1,366	14,606,992		14,952	
BP	722	7,547,768	22	272,851	75.5	36,150	9,163
CN	122	1,328,204	16	160,630	74.7	120,938	31,711
HB	245	2,577,252	8	65,645	60.1	25,471	6,429
HT	13,575	149,478,066	242	2,588,126	57.8	17,314	4,357
RF	344	3,839,675	6	65,666	63.6	17,102	4,303
CT	85,256	812,183,368	1,072	11,454,074	49.9	14,103	3,545
LTGS female	3,008	30,715,293	61	615,782		20,048	
BP	69	573,947	0	-	-	-	-
CN	16	162,800	0	-	-	-	-
HB	32	286,900	0	-	-	-	-
HT	671	7,291,654	18	160,431	66.5	22,002	5,546
RF	7	47,065	0	-	-	-	-
CT	2,213	22,352,927	43	455,351	57.0	20,371	5,132
HRGS female	2,244	22,603,078	46	445,661		19,717	
BP	63	504,664	0	-	-	-	-
CN	16	162,800	0	-	-	-	-
HB	26	239,512	0	-	-	-	-
HT	499	5,474,244	15	139,144	68.5	25,418	6,416
RF	7	47,065	0	-	-	-	-
CT	1,633	16,174,793	31	306,517	60.8	18,950	4,772

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; WELL state: subjects without any prior osteoporosis and osteoporotic fractures; Wtd=weighted; Unwtd=unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group;

**Rates per 1,000,000 person-years.

Table 4.2.6 Incidence of first osteoporotic fracture in women with prior osteoporosis by type of glucocorticoid use and treatment group, MEPS 1996-2004

Female	GIOP state		1st Fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS female	1,480	15,408,082	74	846,057		54,910	
BP	497	5,402,484	19	240,751	79.1	44,563	11,332
CN	87	1,097,498	0	-	-	-	-
HB	146	1,680,494	6	78,904	62.5	46,953	11,951
HT	128	1,185,942	2	16,124	71.3	13,596	3,416
RF	68	678,515	2	22,569	76.4	33,262	8,421
CT	554	5,363,149	45	487,709	72.7	90,937	23,553
LTGS female	141	1,491,522	6	94,505		63,361	
BP	43	492,065	0	-	-	-	-
CN	4	72,069	0	-	-	-	-
HB	8	101,944	0	-	-	-	-
HT	26	216,683	0	-	-	-	-
RF	4	38,280	0	-	-	-	-
CT	56	570,481	6	94,505	59.1	165,658	44,268
HRGS female	120	1,246,176	6	94,505		75,836	
BP	37	409,344	0	-	-	-	-
CN	4	72,069	0	-	-	-	-
HB	4	31,143	0	-	-	-	-
HT	22	193,353	0	-	-	-	-
RF	4	38,280	0	-	-	-	-
CT	49	501,987	6	94,505	59.1	188,262	50,808

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group;

**Rates per 1,000,000 person-years.

Table 4.2.7 Incidence of repeated osteoporotic fracture in women with prior fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Female	GIFX state		Repeated fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS female	1,388	14,734,044	140	1,393,347		94,567	
BP	70	759,690	20	238,788	74.5	314,323	90,024
CN	29	334,481	4	29,314	75.5	87,640	22,669
HB	13	129,162	6	60,746	61.2	470,309	146,889
HT	64	638,454	20	172,093	52.9	269,546	75,519
RF	7	65,699	2	27,651	79.5	420,874	127,645
CT	1,205	12,806,558	88	864,755	62.8	67,524	17,326
LTGS female	78	826,558	14	143,055		173,073	
BP	13	133,560	4	56,656	78.7	424,199	128,900
CN	4	46,406	0	-	-	-	-
HB	2	6,719	2	6,719	56.5	1,000,000	-
HT	4	26,143	2	15,806	50.5	604,598	207,024
RF	0	-	0	-	-	-	-
CT	55	613,730	6	63,874	70.2	104,075	27,101
HRGS female	60	604,649	8	69,979		115,735	
BP	11	101,593	2	24,689	70.5	243,019	67,237
CN	4	46,406	0	-	-	-	-
HB	2	6,719	2	6,719	56.5	1,000,000	-
HT	2	10,338	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	41	439,593	4	38,571	78.4	87,743	22,697

Ave.=average; GIFX state: subject with prior osteoporotic fractures;HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=Unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table 4.2.8 Incidence of first osteoporotic fracture in men without prior osteoporosis and fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Male	WELL state		1st Fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS male	81,270	838,077,503	1,309	14,393,420		17,174	
BP	45	482,756	2	10,005	69.6	20,725	5,222
CN	28	248,773	2	9,739	70.5	39,148	9,934
CT	81,197	837,345,974	1,305	14,373,676	39.7	17,166	4,319
LTGS male	2,022	21,376,891	46	586,081		27,417	
BP	18	124,087	0	-	-	-	-
CN	8	64,842	0	-	-	-	-
CT	1,996	21,187,962	46	586,081	55.5	27,661	6,988
HRGS male	1,574	16,706,308	41	539,374		32,286	
BP	16	113,480	0	-	-	-	-
CN	8	64,842	2	9,739	70.5	150,196	39,871
CT	1,550	16,527,986	39	529,635	56.6	32,045	8,109

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; WELL state: subjects without any prior osteoporosis and osteoporotic fractures; Wtd=weighted; Unwtd=Unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table 4.2.9 Incidence of first osteoporotic fracture in men with prior osteoporosis by type of glucocorticoid use and treatment group, MEPS 1996-2004

Male	GIOP state		1st Fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS male	119	1,135,183	4	19,888		17,520	
BP	21	232,678	0	-	-	-	-
CN	8	83,718	2	10,580	78.5	126,377	33,212
CT	90	818,787	2	9,308	80.6	11,368	2,854
LTGS male	17	171,080					
BP	8	91,723	0	-	-	-	-
CN	2	11,380	0	-	-	-	-
CT	7	67,977	0	-	-	-	-
HRGS male	13	115,900					
BP	6	57,101	0	-	-	-	-
CN	2	11,380	0	-	-	-	-
CT	5	47,419	0	-	-	-	-

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=Unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table 4.2.10 Incidence of repeated osteoporotic fracture in men with prior fracture by type of glucocorticoid use and treatment group, MEPS 1996-2004

Male	GIFX state		Repeated fracture			Incidence (/10^6)**	
GS type Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
MEPS male	1,412	15,504,757	99	1,026,024		66,175	
BP	4	23,320	2	10,005	69.6	429,031	130,733
CN	4	82,435	0	-	-	-	-
CT	1,404	15,399,002	97	1,016,019	49.9	65,980	16,919
LTGS male							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	50	631,608	4	45,527	52.9	72,081	18,529
HRGS male							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	41	542,349	2	12,714	65.3	23,442	5,913

Ave.=average; GIFX state: subject with prior osteoporotic fractures;HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=Unweighted.

§ total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Age plays an important role with respect to incidence rates of osteoporosis and osteoporotic fractures. Appendix B lists 24 tables which provide a further breakdown of incidence rates by four age groups: 11 to 30 years old, 31 to 50 years old, 51 to 70 years old and 71 to 90 years old. Generally speaking, incidence rates of osteoporosis in groups of older ages are likely larger than those in groups of younger ages; however, it is not absolute. A similar trend is not observed for incidence rates of osteoporotic fractures. In some cases, subjects in groups of 51 to 70 years old have relatively higher incidence rates of osteoporotic fractures. It appears that the patterns are inconsistent.

To further investigate the relationships between incidence of osteoporotic fracture and potential factors, such as age, gender and use of glucocorticoid steroids and use of anti-osteoporotic agents, a logistic regression analysis was performed. The next section demonstrates the analysis and results.

4.2.4 Relative Risks of Osteoporotic Fractures

In logistic regression models for this study, all independent variables, except age, are coded by dichotomous values (FX=1 when incidence of osteoporotic fracture was found, otherwise, FX=0; sex=0 for men and sex=1 for women; GS=1 for use of glucocorticoid tablets and GS=0 for non-GS users; BP=1 if use of bisphosphonate and BP=0 for non-users, etc.). Age is treated as continuous variable.

The logistic regression analyses indicated that the use of oral glucocorticoid tablets does not significantly change the odds of osteoporotic fractures in study subjects (relative risk (RR)= 1.146, 95% confidence interval (CI) 0.901-1.458 for subjects in the WELL state; RR=0.55, 95% CI 0.188-1.621 for subjects in the GIOP state; RR=1.241, 95% CI 0.532-2.893 for subjects in GIFX state). Women in the WELL states had significantly lower odds of osteoporotic fractures than men in the same state (RR=0.823, 95% CI 0.723-0.936), whereas the impact of gender on the odds ratio was not significant for subjects in the GIOP and GIFX states (RR=3.266 95% CI 0.638-16.709 for the GIOP state, RR=0.870 95% CI 0.552-1.373 for the GIFX state). The positive coefficient for age indicates that the odds of osteoporotic fractures increase with an increased age (RR=1.016 95% CI 1.013-1.019 for subjects in the WELL state; RR=1.052, 95% CI 1.019-1.087 for subjects in the GIOP state; RR=1.018, 95% CI 1.009-1.028 for subjects

in the GIFX state). Table 4.2.11 shows the logistic regression models, estimates of coefficients for each variable and statistics.

Table 4.2.11 Logistic regression analysis of odds of osteoporotic fractures for state

State* Variable**	Coefficient	$P^{\dagger}$	Odds Ratio		
			Estimate	95% Confidence Interval	
WELL	**Model fit (% correct): 61.1%**				
Intercept	-4.7063	<.0001	-	-	-
GS	0.1364	0.2674	1.146	0.901	1.458
BP	0.4947	0.1378	1.640	0.853	3.152
CN	1.5636	0.0001	4.776	2.158	10.569
HB	0.2128	0.7025	1.237	0.415	3.687
HT	0.0171	0.8811	1.017	0.813	1.273
RF	-0.1592	0.7903	0.853	0.264	2.756
Gender	-0.1950	0.0031	0.823	0.723	0.936
Age	0.0156	<.0001	1.016	1.013	1.019
GIOP	**Model fit (% correct): 70.1%**				
Intercept	-7.2640	<.0001	-	-	-
GS	-0.5935	0.2800	0.552	0.188	1.621
BP	-0.6523	0.1428	0.521	0.218	1.246
CN	-2.3492	0.0327	0.095	0.011	0.824
HB	-0.2770	0.7081	0.758	0.178	3.232
HT	-1.4908	0.1582	0.225	0.028	1.785
RF	-0.7888	0.4608	0.454	0.056	3.696
Gender	1.1835	0.1553	3.266	0.638	16.709
Age	0.0510	0.0021	1.052	1.019	1.087
GIFX	**Model fit (% correct): 61.1%**				
Intercept	-3.5530	<.0001	-	-	-
GS	0.2158	0.6172	1.241	0.532	2.893
BP	1.5250	0.0006	4.595	1.918	11.007
CN	-0.4224	0.5378	0.655	0.171	2.513
HB	2.4245	0.0090	11.296	1.834	69.585
HT	1.7343	0.0031	5.665	1.795	17.877
RF	2.0400	0.0728	7.690	0.828	71.438
Gender	-0.1388	0.5507	0.870	0.552	1.373
Age	0.0180	0.0002	1.018	1.009	1.028

Estimation of logit using maximum likelihood method.
Incidence of osteoporotic fractures (yes=1, no=0); gender (male=0, female=1).
*WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures.
**variable (yes=1, no=0): BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
† Probability (Wald's Chi-Square).

The impact of glucocorticoid use on osteoporotic fractures for subjects in the GIOP state (RR=0.55, 95% CI 0.188-1.621) does not match the findings in the literature that glucocorticoid use increases fracture risks. Table 4.2.12 shows weighted number and charactieristics of subjects by glucocorticoid use and Markov state. The average age of subjects in the GIOP state was 68.7 years old. Therefore, a possible reason for the low odds ratio is that subjects in the GIOP state tend to be aware of osteoporosis and be receiving pharmacologic or non-pharmacologic strategies that prevent the occurance of osteoporotic fractures. Further investigation on confounding factors is needed.

Table 4.2.12 Weighted number and age of subjects by state

State/	Unwtd.	Weighted		Weighted averages		
GS use/ gender	N	N	Age	Cum. GS dose	Cum. quantity of GS tablets	Daily GS dose
WELL	181,581	1,815,341,765	37.7			
GS	10,126	106,748,184	45.1	900.7	118.1	10.8
Male	4,166	45,048,318				
Female	5,960	61,699,866				
No GS	171,442	1,708,593,581	37.2	-	-	-
Male	77,146	793,423,785				
Female	94,296	915,169,796				
GIOP	1,597	16,522,541	68.7			
GS	210	2,186,312	67.8	1,602.5	333.0	10.6
Male	19	190,149				
Female	191	1,996,163				
No GS	1,387	14,336,229	68.9	-	-	-
Male	100	945,034				
Female	1,287	13,391,195				
GIFX	2,798	30,218,056	46.8			
GS	200	2,346,937	53.6	1,521.5	202.0	10.3
Male	90	1,149,352				
Female	110	1,197,585				
No GS	2,598	27,871,119	46.3	-	-	-
Male	1,322	14,355,405				
Female	1,276	13,515,714				

Cum.=cumulative; GS=glucocorticoid steroids; Unwtd.=unweighted.

Although no significant impact of glucocorticoid use on osteoporotic fractures was found, relative risks of osteoporotic fractures for subjects in MEPS were used to estimate missing values of incidence rates of osteoporotic fractures in Section 4.2.3. Information derived from the MEPS data provided the best estimate for the missing values. Table 4.2.13 shows expected probabilities of osteoporotic fractures for subjects with different sets of independent variables. By comparing probabilities in non-glucocorticoid users to those in glucocorticoid users for the same set of other independent variables, relative risks of osteoporotic fractures in glucocorticoid use are calculated. The relative risks are listed in Table 4.2.14. The relative risks are consistent across different treatments for subjects in the same state, and demonstrate the overall harmful effects of glucocorticoid use on osteoporotic fractures for subjects in the WELL and GIFX states and protective effects for subjects in the GIOP state.

Table 4.2.13 Predicted one-year probability of osteoporotic fractures for subjects based on logistic regression by gender, type of treatment, subject's state and age

State*		1-Year probability (/10^6)†								
		Treatment for women**						Treatment for men**		
Age	GS use	BP	CN	HB	HT	RF	CT	BP	CN	CT
WELL										
30	*No*	13525	38394	10237	8432	7079	8291	16389	46278	10058
	Yes	15471	43760	11715	9653	8105	9491	18740	52685	11511
50	*No*	14606	41380	11058	9110	7649	8957	17695	49845	10865
	Yes	16705	47142	12653	10428	8757	10253	20229	56717	12433
70	*No*	15772	44587	11944	9842	8264	9677	19103	53672	11736
	Yes	18036	50772	13666	11264	9461	11075	21834	61037	13428
90	*No*	16389	46278	12413	10229	8590	10058	19848	55688	12197
	Yes	18740	52685	14202	11707	9833	11511	22683	63311	13955
GIOP										
30	*No*	1743	320	2535	754	1521	3341	534	98	1026
	Yes	964	177	1402	417	841	1849	295	54	567
50	*No*	2248	413	3269	973	1962	4308	690	126	1323
	Yes	1243	228	1808	538	1085	2384	381	70	731
70	*No*	2900	533	4215	1256	2531	5552	890	163	1707
	Yes	1604	294	2332	694	1399	3075	492	90	943
90	*No*	3293	605	4785	1426	2874	6302	1010	185	1938
	Yes	1821	334	2649	788	1589	3491	558	102	1072
GIFX										
30	*No*	115904	18357	243737	139134	179933	27739	130903	21033	31738
	Yes	139915	22678	285672	167047	213997	34191	157467	25967	39083
50	*No*	125450	20051	260706	150268	193598	30272	141486	22968	34623
	Yes	151100	24761	304386	179948	229524	37291	169778	28344	42607
70	*No*	135662	21898	278423	162125	208037	33028	152775	25077	37760
	Yes	163010	27030	323770	193613	245826	40660	182844	30930	46433
90	*No*	141025	22883	287553	168331	215548	34496	158691	26201	39430
	Yes	169243	28239	333699	200736	254264	42452	189663	32308	48467

† per 1,000,000 person-years.

*WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures.

**Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

Table 4.2.14 Relative risks of osteoporotic fractures within one year in glucocorticoid users versus non-glucocorticoid users by gender, type of treatment, subject's state and age

State*	**Relative risk of osteoporotic fractures within one year**								
	Treatment for women**						**Treatment for men****		
Age	**BP**	**CN**	**HB**	**HT**	**RF**	**CT**	**BP**	**CN**	**CT**
WELL									
30	1.1439	1.1397	1.1444	1.1447	1.1450	1.1448	1.1434	1.1384	1.1455
50	1.1437	1.1393	1.1443	1.1446	1.1449	1.1446	1.1432	1.1379	1.1443
70	1.1435	1.1387	1.1441	1.1445	1.1448	1.1445	1.1429	1.1372	1.1442
90	1.1434	1.1384	1.1441	1.1444	1.1447	1.1445	1.1428	1.1369	1.1441
GIOP									
30	0.5528	0.5525	0.5530	0.5526	0.5528	0.5532	0.5525	0.5524	0.5526
50	0.5529	0.5525	0.5532	0.5526	0.5529	0.5535	0.5526	0.5524	0.5527
70	0.5531	0.5525	0.5534	0.5527	0.5530	0.5538	0.5526	0.5524	0.5528
90	0.5532	0.5525	0.5536	0.5527	0.5531	0.5540	0.5526	0.5524	0.5529
GIFX									
30	1.2072	1.2354	1.1720	1.2006	1.1893	1.2326	1.2029	1.2346	1.2314
50	1.2145	1.2349	1.1675	1.1975	1.1856	1.2319	1.2000	1.2340	1.2306
70	1.2016	1.2343	1.1629	1.1942	1.1816	1.2311	1.1968	1.2334	1.2297
90	1.2001	1.2341	1.1605	1.1925	1.1796	1.2306	1.1952	1.2335	1.2292

*WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures.

**Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

4.3 ECONOMIC OUTCOMES

This section shows national estimates of average direct medical costs associated with osteoporosis, osteoporotic fractures and treatments according to MEPS data from 1996 to 2004. Detailed definitions of costs are described in Chapter 3. The unadjusted costs represent original values reported in MEPS. All costs have been adjusted to 2005 U.S. dollars based on the medical component of the Consumer Price Index (CPI) for comparisons. The results of this section address the third and fourth study objectives.

Table 4.3.1 shows average total direct medical costs associated with anti-osteoporosis treatments in MEPS data from 1996 to 2004. The total costs of anti-osteoporotic treatments include expenses for prescribed medicines, expenses for medical events associated with new osteoporosis and osteoporotic fractures, expenses for outpatient visits and office-based medical provider visits associated with the anti-osteoporotic treatment, and expenses of medical events and prescribed medicines associated with treatments of adverse drug events. Because each subject was followed for two years, these costs likely reflect total costs of an anti-osteoporotic treatment for two years. These costs were used to calculate the short-term (two-year) cost-effectiveness ratio for anti-osteoporotic treatments in Section 4.5.

Among women in the BP, CN and HT groups, glucocorticoid users have higher average total direct medical costs than all female MEPS subjects. Men in the BP groups have similar average total direct medical costs. Female glucocorticoid users in the HB and RF groups and male glucocorticoid users in the CN group have relatively lower average total direct medical costs. This phenomenon may be explained by a relatively large variance due to small sample size in these groups.

Table 4.3.1 Average total costs of anti-osteoporosis treatments per subject by gender and type of subject

Gender		All					Men					Women				
	Cost*	Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§	
Type†	Subject**	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE
BP	MEPS	1,072	701.2	42.5	816.2	50.8	67	409.7	30.5	488.5	35.6	1,005	721.3	45.5	838.8	54.3
	LTGS	126	733.9	37.7	850.0	44.1	23	395.7	25.8	475.5	33.9	103	804.7	43.3	928.4	50.2
	HRGS	107	803.0	35.8	926.5	41.9	21	394.0	28.5	466.8	37.2	86	899.8	38.1	1,035.2	44.3
CN	MEPS	148	548.2	63.7	671.0	75.6	21	910.2	24.8	1,086.6	30.5	127	499.6	37.1	615.3	48.4
	LTGS	18	696.8	71.8	882.4	81.7	5	629.3	126.3	819.7	167.6	13	771.6	64.1	896.1	67.0
	HRGS	18	696.8	71.8	882.4	81.7	5	629.3	126.3	819.7	167.6	13	771.6	64.1	896.1	67.0
HB	MEPS											330	767.5	143.9	915.2	181.4
	LTGS											32	773.2	25.5	875.5	31.1
	HRGS											25	715.8		809.7	
HT	MEPS											8,654	414.3	7.8	516.7	9.8
	LTGS											404	504.3	47.5	631.0	59.4
	HRGS											299	434.4	20.7	549.3	26.5
RF	MEPS											303	878.9	44.5	1,010.3	49.6
	LTGS											11	861.4	96.9	963.9	114.0
	HRGS											10	889.5	101.2	994.2	119.0

*Total costs include expenses for prescribed medicines, expenses for medical events linked to new osteoporosis and osteoporotic fractures, expenses for outpatient visits and office-based medical provider visits linked to prescriptions but not linked to osteoporosis and osteoporotic fractures, and expenses of medical events and prescribed medicines linked to treatments of adverse drug events.

§Costs are adjusted to 2005 dollars based on the medical component of the Consumer Price Index (CPI).

†Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneous use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. SE=standard error of the mean; Unwtd=unweighted.

Table 4.3.2 shows the average total costs per incidence of osteoporotic fracture, and the average total three-month costs of medical events per subject with osteoporosis. The total costs include expenses for medical events linked to an episode of osteoporosis or osteoporotic fracture, and expenses for prescribed medicines linked to the episode, but exclude expenses for medical events linked to anti-osteoporotic treatments. It is noted that the unit for osteoporosis is per subject per three months and that the unit for osteoporotic fractures is per episode. Average costs of osteoporosis are higher in both male and female glucocorticoid users than in all MEPS subjects. Compared to values in corresponding MEPS subjects, costs per osteoporotic fracture in glucocorticoid users are not significantly different. The extreme costs of repeated fractures may not be representative because of small sample sizes.

Table 4.3.3 shows the average three-month costs per subject of anti-osteoporotic treatments. The total costs include expenses for prescribed medicines, expenses for outpatient visits and office-based medical provider visits linked to prescriptions, and expenses of all medical events for treatments for adverse drug events. It is noted that the unit for anti-osteoporotic treatments is per subject per three months. Analysis of variance (ANOVA) of these costs indicates significant differences in average direct medical costs of preventive anti-osteoporotic treatments for glucocorticoid users among treatments (for men and women, df=5, F=43.55, $p< 0.0001$, specifically, $p=0.0021$ for BP, $p< 0.0001$ for CN, $p=0.0014$ for HB, $p<0.0001$ for HT) when comparing to costs of the RF group. Therefore, all hypotheses for the fourth study objective were rejected.

Table 4.3.4 shows the average prescription costs per subject for a three-month supply of anti-osteoporotic agents. Cost information in Table 4.3.2 and Table 4.3.3 were used in Markov modeling to estimate long-term costs associated with an episode of osteoporotic fracture and monitoring costs for osteoporosis in Section 4.5.

Table 4.3.2 Average total costs per episode of osteoporotic fracture and average total three-month costs per subject with osteoporosis by gender and type of subject

Gender		All					Men					Women				
	Cost*	Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§	
Type†	Subject**	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE
Per subject per 3 months																
OP	MEPS	392	150.4	18.7	183.2	22.3	14	398.7		530.4		378	142.6	19.0	172.2	22.0
	LTGS	47	295.7	21.0	347.9	24.3	5	530.9		705.6		42	273.8	22.5	314.6	26.2
	HRGS	37	377.7	29.5	441.1	34.6	4	818.8		1,086.0		33	341.4	31.5	388.0	36.9
Per fracture episode																
FS	MEPS	1,591	4,369.5	417.6	5,299.8	522.7	745	3,654.6	524.6	4,363.2	608.7	846	5,018.3	637.9	6,149.8	827.2
	LTGS	74	4,053.7	382.5	4,933.4	443.4	29	4,483.1	131.9	5,704.0	167.5	45	3,781.3	620.0	4,444.5	709.9
	HRGS	59	4,139.1	476.7	5,033.0	552.2	24	4,233.5	155.7	5,325.7	185.1	35	4,074.3	805.3	4,832.0	924.9
FR	MEPS	29	8,184.3	1,203.6	9,100.1	1,332.6	1	39.0		49.4		28	8,366.2	1,235.3	9,302.2	1,367.8
	LTGS	5	6,710.3		7,653.6		0					5	6,710.3		7,653.6	
	HRGS	2	19,158.0		21,661.0		0					2	19,158.0		21,661.0	

§Costs are adjusted to 2005 dollars based on the medical component of the Consumer Price Index (CPI).

*Total costs include expenses for medical events linked to an episode of osteoporosis or osteoporotic fracture, and expenses for prescribed medicines linked to the episode, but exclude expenses for medical events linked to anti-osteoporotic treatments.

†FS=new episode of first-time osteoporotic fractures; FR=new episode of repeated osteoporotic fractures; OP=new episode of osteoporosis.

**HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. SE=standard error of the mean; Unwtd=unweighted.

Table 4.3.3 Average three-month costs of anti-osteoporotic treatments by gender and type of subject

Gender		All					Men					Women				
3-Month Tx*		Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§		Unwtd	Un-adjusted		2005 $§	
Type†	Subject**	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE	N	Mean	SE	Mean	SE
BP	MEPS	1072	83.3	3.3	97.0	4.1	67	51.7	3.4	61.9	3.9	1005	85.6	3.6	99.5	4.4
	LTGS	126	71.2	4.1	84.8	4.8	23	51.7	3.4	62.9	4.5	103	75.2	4.9	89.4	5.7
	HRGS	107	75.7	3.5	90.1	4.2	21	51.8	3.8	62.2	4.9	86	81.4	4.2	96.8	4.9
CN	MEPS	148	60.6	4.4	74.7	5.7	21	53.7	2.5	66.5	3.4	127	61.6	4.9	75.9	6.4
	LTGS	18	92.6	8.4	117.2	9.4	5	85.1	9.1	111.0	12.0	13	94.2	9.0	118.5	9.5
	HRGS	18	92.6	8.4	117.2	9.4	5	85.1	9.1	111.0	12.0	13	94.2	9.0	118.5	9.5
HB	MEPS											330	78.5	3.5	92.3	3.8
	LTGS											32	96.6	3.2	109.4	3.9
	HRGS											25	89.5		101.2	
HT	MEPS											8652	51.6	0.9	64.3	1.2
	LTGS											404	63.1	6.0	78.9	7.5
	HRGS											299	54.0	2.5	68.2	3.2
RF	MEPS											303	107.1	5.4	123.1	6.0
	LTGS											11	106.8	12.2	119.7	14.4
	HRGS											10	110.6	12.8	123.7	15.1

§Costs are adjusted to 2005 dollars based on the medical component of the Consumer Price Index (CPI).

* The total costs include expenses for prescribed medicines, expenses for outpatient visits and office-based medical provider visits linked to prescriptions, expenses for medical events linked to new osteoporosis and osteoporotic fractures, and expenses of all medical events for treatments for adverse drug events.

**HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. SE=standard error of the mean; Unwtd=unweighted.

†Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneous use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

Table 4.3.4 Average prescription costs for three-month supply of anti-osteoporotic agents by gender and type of subject

Gender		All					Men					Women				
3-Month Rx* Type†	Unwtd Subject**	Un-adjusted N	2005 $§ Mean	SE	Unwtd Mean	SE	Un-adjusted N	2005 $§ Mean	SE	Unwtd Mean	SE	Un-adjusted N	2005 $§ Mean	SE	2005 dollar§ Mean	SE
BP	MEPS	1,072	69.7	2.3	81.1	2.8	65	42.6	3.4	50.8	3.8	1,007	71.6	2.5	83.2	3.0
	LTGS	126	62.4	3.7	74.6	4.4	23	35.4	2.8	43.7	3.8	103	68.1	4.3	81.1	5.1
	HRGS	107	65.5	3.3	78.3	3.9	21	35.2	3.1	43.2	4.2	86	72.8	3.7	86.8	4.4
CN	MEPS	148	50.3	4.0	61.8	4.9	21	44.5	2.8	55.5	3.8	127	51.1	4.3	62.8	5.5
	LTGS	18	73.2	7.3	92.0	8.1	5	77.0	11.3	99.9	15.1	13	72.4	6.2	90.3	6.1
	HRGS	18	73.2	7.3	92.0	8.1	5	77.0	11.3	99.9	15.1	13	72.4	6.2	90.3	6.1
HB	MEPS											330	59.5	2.5	69.8	2.8
	LTGS											32	62.5	2.1	71.8	2.7
	HRGS											25	46.3		53.7	
HT	MEPS											8,654	39.7	0.5	49.3	0.6
	LTGS											404	45.5	2.2	56.7	2.7
	HRGS											299	44.0	2.2	55.6	2.9
RF	MEPS											303	95.0	5.0	109.1	5.6
	LTGS											11	97.1	12.0	109.3	14.1
	HRGS											10	100.5	12.6	112.9	14.7

§Costs are adjusted to 2005 dollars based on the medical component of the Consumer Price Index (CPI).

*Average total costs of prescriptions per subject per three months; costs include expenses of prescriptions only.

**HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey. SE=standard error of the mean; Unwtd=unweighted.

†Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneous use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

4.4 LONG-TERM ESTIMATES OF COSTS AND EFFECTIVENESS

This section shows estimates of long-term costs and incidence rates of osteoporosis and osteoporotic fractures in glucocorticoid tablet users in each of the following groups: bisphosphonates (BP), calcitonin (CN), control (CT), HRT-bisphosphonate combination (HB), hormone replacement therapy (HT) and raloxifene (RF). The long-term estimates are obtained from Markov modeling with model inputs derived from Section 4.1 to Section 4.3. It is noted that annual incidence rates of osteoporosis and osteoporotic fractures must be converted to three-month transition probabilities to fit the need of Markov modeling. The following paragraphs describe the transformation and model inputs.

4.4.1 Model inputs

Model inputs for costs are listed in Table 4.3.2 and Table 4.3.3. Based on Tables A.1 to A.24 in Appendix B, annual incidence rates of osteoporosis and osteoporotic rates are converted to three-month transition probabilities for subjects in different states and age groups. The results are shown in Table 4.4.1, and data sources are marked for each entry. In order to directly apply the transition probabilities in Markov modeling, the average age of subjects for that transition probability is multiplied by four to get an index used in tables of transition probabilities in the modeling. In other words, four Markov cycles match one year of age. Information from Appendix B is marked as source a, b and c when sources are based on HRGS users, LTGS users and all MEPS subjects, respectively. However, these sources do not provide direct information on some transition probabilities among Markov states; therefore, information on relative risks described in Section 4.2.4 was used.

Compared to female non-glucocorticoid users in the WELL state, the relative risk (RR) of any osteoporotic fracture in female glucocorticoid users is approximately 1.14. Similarly, relative risks for subjects in the GIOP and GIFX states and for men are found in Table 4.2.14. Each entry marked as "c, d" "c, f" and "c, g" in Table 4.4.1 and Table 4.4.3 is carefully matched with the corresponding age (i.e., index), treatment group and state in the logistic regression models demonstrated in Section 4.2.4; therefore, the actual value of relative risks for calculations may be more or less than 1.14.

Some expected values of probabilities obtained from logistic regression models were used for the lower limits (i.e., age=30 or index=120) because the study model used interpolation in tables of transition probabilities to estimate proper values for model simulations. These estimates are marked as "e" in Tables 4.4.1 and 4.4.3. For transition probabilities in the CN group from the GIOP to the FX state, no information is available for females in Appendix B. To estimate this transition probability for the female CN group, relative risks of osteoporotic fractures between men and women were evaluated. The logistic regression models demonstrate that the relative risks of osteoporotic fractures for female glucocorticoid users in the GIOP state are approximately 0.31 when males at the same age and GIOP state are the comparator. Accordingly, three-month transition probabilities for the female CN group were obtained, which was marked as an "h" in Table 4.4.1. Bolded values in Tables 4.4.1 and 4.4.2 were used in model simulations.

Table 4.4.1 Three-month transition probabilities among Markov states for the base case in female glucocorticoid users

State*	WELL To GIOP			WELL To FX			GIOP To FX			GIFX To FX		
Option†	Age	3m Prob.	Note	Age	3m Prob.	Note	Age	3m Prob.	Note	Age	3m Prob.	Note
BP	41	**.104407**	a, b	30	**.003890**	e	30	**.000241**	e	66	.267789	c
	64	**.159686**	a, b	66	.007880	c	65	**.000938**	c, f	66	**.325648**	c, g
	75	**.026372**	b	66	**.009019**	c, d	65	.001697	c	70	**.235180**	a, b
	77	**.021654**	a	81	.011983	c	80	**.010617**	c, f	71	**.047260**	a
				81	**.013714**	c, d	80	.019203	c,	81	.068907	c
										81	**.138008**	b
CN	40	**286498**	a, b	30	**.011124**	e	30	**.000044**	e	30	**.005718**	e
	64	**.184727**	a, b	70	.033932	c	81	**.010556**	h	76	.027317	c
	65	.057766	c	70	**.038733**	c, d				76	**.033782**	c, g
	72	**.121481**	a, b	78	.032501	c						
				78	**.037094**	c, d						
HB	65	.047499	b	30	**.002942**	e	50	**.033459**	c, f	57	.037196	c
	65	**.054715**	a	49	.030141	c	50	.060517	c	57	**.044322**	c, g
	79	.352460	b	49	**.034511**	c, d	54	**.001948**	c, f	57	.900000	b
	79	**.440052**	a	59	.005090	c	54	.003523	c	79	.140824	c
				59	**.005828**	c, d	79	**.009000**	c, f	79	**.167290**	c, g
				83	.003639	c	79	.016272	c			
				83	**.004166**	c, d						
HT	14	**.007762**	b	42	**.004343**	a	30	**.000104**	e	45	.114370	c
	66	**.004292**	a	44	.004517	b	71	**.006882**	c, f	45	**.138791**	c, g
	74	.017822	b	53	**.001550**	a	71	.012455	c	50	**.135641**	b
	74	**.016917**	a	54	.001969	b				52	.061588	c
				77	.026469	b				52	**.074692**	c, g
				77	**.029449**	a				78	.150593	c
										78	**.182195**	c, g
RF	48	**.014695**	c	30	**.002033**	e	30	**.000210**	e	30	**.058422**	e
	63	**.052950**	c	58	.004391	c	77	**.009122**	c, f	80	.166790	c
	76	**.053764**	c	58	**.005029**	c, d	77	.016501	c	80	**.200317**	c, g
				73	.005112	c						
				73	**.005855**	c, d						
CT	16	**.002481**	a	13	**.003884**	a	42	.096298	b	39	.016893	c
	16	.001774	b	16	**.004601**	b	42	**.099596**	a	39	**.020822**	c, g
	39	**.002337**	a	42	**.003475**	b	60	**.045284**	a, b	64	**.101248**	b
	39	.001664	b	46	**.001940**	a	78	.015528	b	68	**.046352**	a
	64	.005349	b	64	.002797	b	78	**.018692**	a	84	.027098	c
	64	**.007370**	a	64	**.003880**	a				90	.018738	b
	78	**.023108**	a	80	**.011491**	a				90	**.023795**	a
	79	.022739	b	81	.012578	b						

* Bolded values were used in modeling; WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures.
†BP=bisphosphonate; CN=calcitonin; CT=controls without using any anti-osteoporotic agent; HB=use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene.
a. From MEPS data (1996-2004) related to subjects who used glucocorticoid tablets at accumulated dose of 450 mg or more.
b. From MEPS data (1996-2004) related to subjects who used glucocorticoid tablets for at least three months.
c. From MEPS data (1996-2004) related to subjects who used anti-resorptive agents for at least three months.
d. Compared to non-glucocorticoid female users in the WELL state, the relative risk of any fracture in glucocorticoid users is 1.14.
e. Expected 3-month probabilities calculated based on the logistic regression equation and conversion.
f. Compared to non-glucocorticoid female users in the GIOP state, the relative risk of any fracture in glucocorticoid users is 0.55.
g. Compared to non-glucocorticoid female users in the GIFX state, the relative risk of any fracture in glucocorticoid users is 1.23.
h. Data is not available for women. Compared to male oral glucocorticoid users in the GIOP state at the same age, the relative risk of any fracture in females is 0.31.

Table 4.4.2 Three-month transition probabilities among Markov states for the base case in male glucocorticoid users

State*	WELL To GIOP			WELL To FX			GIOP To FX			GIFX To FX		
Option†	Age	3m Prob.	Note	Age	3m Prob.	Note	Age	3m Prob.	Note	Age	3m Prob.	Note
BP	62	.235177	b	30	**.004718**	e	30	**.000074**	e	30	**.041931**	e
	63	**.235177**	a	70	.010070	c	90	**.000159**	e	90	**.053278**	e
	73	.037773	b	70	**.011522**	c, d						
	73	**.049864**	a									
CN	90	**.032236**	c	30	**.013440**	e	30	**.000014**	e	30	**.006556**	e
				70	**.017661**	a	81	**.034200**	c, f	90	**.008545**	e
				71	**.085906**	a, b						
CT	47	**.000985**	b	24	.003132	b	27	**.007683**	g	43	**.025077**	b
	57	.000923	b	27	**.003073**	a	38	**.020723**	g	65	.012416	b
	57	**.001175**	a	38	**.008289**	a	60	**.027858**	g	65	**.014069**	a
	72	.001508	b	39	.007166	b	80	**.022918**	g			
	72	**.001833**	a	59	.009940	b						
				60	**.011143**	a						
				80	.007517	b						
				80	**.009167**	a						

Bolded values were used in modeling.
*WELL state: subjects without any prior osteoporosis and osteoporotic fractures; GIOP state: subjects with prior osteoporosis but without prior osteoporotic fractures; GIFX state: subject with prior osteoporotic fractures.
†BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; Index=average age multiplied by four.
a. From MEPS data (1996-2004) related to subjects who used glucocorticoid tablets at cumulative dose≧ 450 mg.
b. From MEPS data (1996-2004) related to subjects who used glucocorticoid tablets for at least three months.
c. From MEPS data (1996-2004) related to subjects who used anti-resorptive agents for at least three months.
d. Compared to non-glucocorticoid users, the relative risk (RR) of any fracture in female oral glucocorticoid users from the WELL state is 1.14; the expected RR match with rx type, age and gender.
e. Expected 3-month probabilities calculated based on the logistic regression equation and conversion.
f. Compared to non-glucocorticoid users, the relative risk (RR) of any fracture in female oral glucocorticoid users from the GIOP state is 0.55; the expected RR match with rx type, age and gender.
g. Compared to persons with normal BMD, the risk of any osteoporotic fracture is increased 2.5-fold in men with BMD t-score < -2.5; Kanis *et al.* (2001) *Osteoporosis Int* 12: 989-995.

4.4.2 Estimates of Long-Term Outcomes

Long-term costs and effectiveness are estimated based on the Markov model for six hypothetical cohorts: male or female glucocorticoid users at an age of 30, 50 or 65 years old. Estimates are generated by the first-order and second-order Monte Carlo simulations for 10,000 samples at three different lengths of anti-osteoporotic treatment: two years, 10 years and life time. Prior exposure to osteoporosis and/or osteoporotic fractures are introduced by assigning subjects of each hypothetical cohort to different

Markov states based on percentages listed in Table 4.2.2. Costs are adjusted to 2005 dollars based on an annual discount rate of 5% for all base cases. Effectiveness represents percentage of osteoporotic fractures avoided (full protective effect=1, no protective effect=0) and is not discounted by time. Tables 4.4.3 to 4.4.8 list average cost and average effectiveness for each of six hypothetical cohorts by length of treatment. Significant differences tested by Tukey's method at an alpha level of 0.001 are indicated.

Table 4.4.3, Table 4.4.4 and Table 4.4.5 list long-term estimates for hypothetical cohorts of female glucocorticoid users. Common findings for these female cohorts are described as follows. Within the same age cohort, the longer the length of treatment, the more the total costs, the less the overall effectiveness of the treatment. Bisphosphonate (BP) therapy is the most costly treatment in women with two-year or 10-year simulations, but is not the most expensive treatment for 65-year-old women in the lifetime estimations. Hormone replacement therapy (HT), except for the control group, is the least costly anti-osteoporotic treatments in women for all three lengths of simulations.

Not all long-term costs increase with increased ages. The two-year costs are similar among three female cohorts with ages of 30, 50 and 65 years old, and the same pattern applies to the 10-year estimates of costs among these cohorts. The pattern for lifetime estimates of costs is unclear with respect to age. The long-term effectiveness does not decrease with increased ages. Apparently, the 30-year-old female cohort has relatively lower estimates of lifetime effectiveness than other age cohorts. Theoretically, younger subjects may go through more cycles than older ones, and an increased number of cycles may increase the chance of osteoporotic fractures.

Significant differences in average costs and effectiveness among anti-osteoporotic treatments are indicated in each table. Specifically, Table 4.4.3 shows estimates of long-term costs and effectiveness for 30-year-old female glucocorticoid users.

Significant differences in average costs were found for 10-year and lifetime simulations. Significant differences in average effectiveness were found for lifetime simulations. Therefore, study hypotheses Ho_{5A1}, $Ho_{5B1}$and Ho_{5D1} were rejected.

Table 4.4.3 Estimates of long-term costs and effectiveness for 30-year-old women

Length of estimation **Treatment**	**Cost**[§]	**SD**	**Eff.**[†]	**SD**
2 years				
BP	$4,541	$527	0.9603	0.0041
CN	$4,249	$408	0.9885	0.0011
HB	$2,782	$299	0.9701	0.0047
HT	$1,188	$117	0.9823	0.0025
RF	$3,048	$328	0.9906	0.0012
CT	$534	$86	0.7542	0.0261
10 years				
BP	$18,500[a b c d e f]	$2,124	0.9241[a b c d e f]	0.0077
CN	$16,246[a b c d e f]	$1,542	0.9567[a b c d e f]	0.0052
HB	$15,442[a b c d e f]	$1,857	0.8987[a b c d e f]	0.0159
HT	$6,646[a b c d e f]	$857	0.9320[a b c d e f]	0.0100
RF	$12,103[a b c d e f]	$1,339	0.9590[a b c d e f]	0.0054
CT	$2,217[a b c d e f]	$318	0.3266[a b c d e f]	0.0396
Lifetime				
BP	$43,618[a b c d e f]	$4,941	0.4310[a b c d e f]	0.0629
CN	$38,137[a b c d e f]	$3,779	0.4172[a b c d e f]	0.0618
HB	$40,505[a b c d e f]	$4,743	0.1702[a b c d e f]	0.0564
HT	$25,783[a b c d e f]	$3,387	0.3061[a b c d e f]	0.0617
RF	$36,359[a b c d e f]	$4,434	0.3161[a b c d e f]	0.0696
CT	$4,822[a b c d e f]	$649	0.0050[a b c d e f]	0.0033

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
[a] $p<0.05$ compared to BP; [b] $p<0.05$ compared to CN; [c] $p<0.05$ compared to HB; [d] $p<0.05$ compared to HT; [e] $p<0.05$ compared to RF, [f] $p<0.05$ compared to CT.

Table 4.4.4 shows estimates of long-term costs and effectiveness for 50-year-old female glucocorticoid users. Significant differences in average costs and effectiveness were found for two-year and 10-year simulations. No significant differences in average costs and effectiveness were found for lifetime simulations. Therefore, study hypotheses Ho_{5A1} and Ho_{5C1} were rejected.

Table 4.4.4 Estimates of long-term costs and effectiveness for 50-year-old women

Length of estimation Treatment	**Cost**[§]	**SD**	**Eff.**[†]	**SD**
2 years				
BP	$5,752[a b c d e f]	$772	0.9297[a b c d e f]	0.0076
CN	$4,495[a b c d e f]	$472	0.9804[a b c d e f]	0.0021
HB	$3,522[a b c d e f]	$438	0.9637[a b c d e f]	0.0047
HT	$1,049[a b c d e f]	$88	0.9863[a b c d e f]	0.0019
RF	$3,275[a b c d e f]	$369	0.9846[a b c d e f]	0.0022
CT	$545[a b c d e f]	$90	0.7538[a b c d e f]	0.0260
10 years				
BP	$22,664[a b c d e f]	$2,959	0.8815[a b c d e f]	0.0133
CN	$17,167[a b c d e f]	$1,748	0.9390[a b c d e f]	0.0084
HB	$15,469[a b c d e f]	$1,730	0.9196[a b c d e f]	0.0125
HT	$6,356[a b c d e f]	$811	0.9249[a b c d e f]	0.0111
RF	$14,530[a b c d e f]	$1,776	0.9330[a b c d e f]	0.0108
CT	$2,968[a b c d e f]	$480	0.3297[a b c d e f]	0.0406
Lifetime				
BP	$46,263	$5,659	0.4287	0.0621
CN	$37,090	$3,794	0.4657	0.0604
HB	$39,080	$4,386	0.3630	0.0690
HT	$27,282	$3,605	0.3439	0.0613
RF	$40,050	$5,104	0.3688	0.0696
CT	$5,851	$802	0.0181	0.0097

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
[a] $p<0.05$ compared to BP; [b] $p<0.05$ compared to CN; [c] $p<0.05$ compared to HB; [d] $p<0.05$ compared to HT; [e] $p<0.05$ compared to RF.

The patterns of significant differences in costs and effectiveness for 65-year-old female glucocorticoid users are different from those for the 50-year-old cohort. Table 4.4.5 shows estimates of long-term costs and effectiveness for 65-year-old female glucocorticoid users. No significant differences in average costs and effectiveness were found for two-year and 10-year simulations. Significant differences in average costs and effectiveness were found for lifetime simulations. Therefore, study hypotheses Ho_{5B1} and Ho_{5D1} were rejected.

Table 4.4.5 Estimates of long-term costs and effectiveness for 65-year-old women

Length of estimation **Treatment**	**Cost**[§]	**SD**	**Eff.**[†]	**SD**
2 years				
BP	$6,346	$879	0.9125	0.0100
CN	$4,602	$516	0.9685	0.0036
HB	$2,890	$282	0.9785	0.0031
HT	$2,004	$295	0.9561	0.0070
RF	$4,437	$583	0.9548	0.0067
CT	$697	$116	0.7546	0.0263
10 years				
BP	$21,165	$2,664	0.8614	0.0197
CN	$17,563	$1,901	0.8873	0.0165
HB	$15,927	$1,675	0.8979	0.0178
HT	$13,523	$2,209	0.8107	0.0312
RF	$20,240	$2,798	0.8335	0.0260
CT	$3,850	$554	0.3590	0.0399
Lifetime				
BP	$39,643[a b c d e f]	$4,982	0.4557[a b c d e f]	0.0626
CN	$33,345[a b c d e f]	$3,640	0.5414[a b c d e f]	0.0561
HB	$35,832[a b c d e f]	$4,079	0.5099[a b c d e f]	0.0677
HT	$32,502[a b c d e f]	$4,734	0.3829[a b c d e f]	0.0634
RF	$41,236[a b c d e f]	$5,745	0.4199[a b c d e f]	0.0662
CT	$6,971[a b c d e f]	$909	0.0711[a b c d e f]	0.0247

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
[a] $p<0.05$ compared to BP; [b] $p<0.05$ compared to CN; [c] $p<0.05$ compared to HB; [d] $p<0.05$ compared to HT; [e] $p<0.05$ compared to RF.

Tables 4.4.6 to 4.4.8 shows estimates of long-term costs and effectiveness in male glucocorticoid users. The patterns for male glucocorticoid users are much clearer. Bisphosphonate (BP) appears relatively more expensive than calcitonin (CN) treatment in two-year and 10-year estimations, but CN is more expensive in the lifetime estimation. Bisphosphonate treatment has less effectiveness on men than calcitonin treatment regardless of age and length of treatment. According to results from Tables 4.4.3 to 4.4.8, at least one statistically significant difference was found in long-term estimates of costs and effectiveness for female and male glucocorticoid users in different lengths of estimations. All hypotheses for the fifth study objective were rejected.

Table 4.4.6 Estimates of long-term costs and effectiveness for 30-year-old men

Length of estimation **Treatment**	**Cost**[§]	**SD**	**Eff.**[†]	**SD**
2 years				
BP	$3,686*	$300	0.9582*	0.0060
CN	$2,722*	$247	0.9696*	0.0039
CT	$449*	$43	0.9473*	0.0068
10 years				
BP	$14,030*	$1,109	0.7645*	0.0265
CN	$12,620*	$1,116	0.8452*	0.0210
CT	$2,270*	$195	0.7117*	0.0359
Lifetime				
BP	$23,855*	$2,049	0.0058*	0.0027
CN	$28,737*	$2,342	0.1985*	0.0347
CT	$4,125*	$239	0.0218*	0.0109

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
* An overall significant difference, $p<0.05$.

Table 4.4.7 Estimates of long-term costs and effectiveness for 50-year-old men

Length of estimation Treatment	Cost[§]	SD	Eff.[†]	SD
2 years				
BP	$3,680*	$294	0.9295*	0.0102
CN	$2,908*	$263	0.9537*	0.0064
CT	$680*	$69	0.9180*	0.0113
10 years				
BP	$13,130*	$1,040	0.6436*	0.0371
CN	$13,098*	$1,119	0.7926*	0.0254
CT	$2,552*	$192	0.5853*	0.0443
Lifetime				
BP	$19,023*	$1,696	0.0094*	0.0042
CN	$26,633*	$2,128	0.2492*	0.0356
CT	$3,700*	$204	0.0554*	0.0204

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
* An overall significant difference, $p<0.05$.

Table 4.4.8 Estimates of long-term costs and effectiveness for 65-year-old men

Length of estimation Treatment	Cost[§]	SD	Eff.[†]	SD
2 years				
BP	$3,754*	$294	0.8612*	0.0194
CN	$3,001*	$270	0.9269*	0.0106
CT	$663*	$65	0.8994*	0.0136
10 years				
BP	$10,985*	$923	0.3604*	0.0473
CN	$13,096*	$1,002	0.6461*	0.0347
CT	$2,182*	$157	0.5595*	0.0432
Lifetime				
BP	$13,281*	$1,350	0.0140*	0.0063
CN	$22,712*	$1,854	0.2929*	0.0394
CT	$3,055*	$167	0.1333*	0.0339

Results of second-order Monte-Carlo simulations, N=10,000.
BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate; C/E=cost-effectiveness ratio; SD=standard deviation.
†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.
* An overall significant difference, $p<0.05$.

4.5 COST-EFFECTIVENESS ANALYSIS

This section compares estimates of long-term costs and effectiveness for male and female glucocorticoid users, and interprets the results of comparisons. Sensitivity analyses are performed for variables with uncertainty. Based on the comparisons, cost-effective options are recommended for the prevention and management of glucocorticoid-induced fractures in glucocorticoid tablet users.

4.5.1 Cost-Effectiveness

Markov cohort analyses generate estimates for base cases by using the model inputs which represent the most likely scenario. An annual discount rate of 5% and values described in Section 4.4.1 were used as model inputs of the base cases for Markov cohort analyses. Tables 4.5.1 to 4.5.6 list model outputs of costs and effectiveness for six hypothetical cohorts by length of treatment. Compared to estimates for the control group, cost-effectiveness ratios (C/E), incremental cost, incremental effectiveness and incremental cost-effectiveness ratio (ICER) are also listed for comparisons in the cost-effectiveness analyses.

Based on information listed in Table 4.5.1, the most cost-effective option is hormone replacement therapy (HT) for 30-year-old female glucocorticoid users in two-year, 10-year and lifetime simulations. Other options that follower are HT-BP combination (HB) and raloxifene therapy (RF) for two-year simulations, raloxifene therapy (RF) for 10-year simulations and calcitonin therapy (CN) and bisphosphonate therapy (BP) for lifetime simulations.

Table 4.5.1 Long-term estimates of cost-effectiveness for 30-year-old women

Length Treatment*	Cost§	Incremental Cost	Effectiveness	Incremental Effectiveness	C/E	ICER
2 years						
BP	$4,541	$4,007	0.9603	0.2061	$4,730	$19,437
CN	$4,249	$3,714	0.9885	0.2344	$4,298	$15,848
HB	$2,782	$2,248	0.9701	0.2159	$2,869	$10,412
HT	$1,188	$654	0.9823	0.2281	$1,210	$2,868
RF	$3,048	$2,513	0.9906	0.2364	$3,077	$10,630
CT	$534	reference	0.7542	reference	$711	-
10 years						
BP	$18,500	$16,283	0.9241	0.5975	$20,025	$27,253
CN	$16,246	$14,029	0.9567	0.6300	$16,984	$22,269
HB	$15,442	$13,225	0.8987	0.5721	$17,205	$23,118
HT	$6,646	$4,429	0.9320	0.6053	$7,137	$7,316
RF	$12,103	$9,886	0.9590	0.6324	$12,622	$15,633
CT	$2,217	reference	0.3266	reference	$6,924	-
Lifetime						
BP	$43,618	$38,795	0.4310	0.4260	$103,516	$91,075
CN	$38,137	$33,315	0.4172	0.4122	$93,384	$80,821
HB	$40,505	$35,682	0.1702	0.1651	$267,380	$216,089
HT	$25,783	$20,961	0.3061	0.3011	$88,629	$69,610
RF	$36,359	$31,536	0.3161	0.3111	$121,283	$101,366
CT	$4,822	reference	0.0050	reference	$1,416,526	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene group.

The most cost-effective option remains hormone replacement therapy (HT) for 50-year-old female glucocorticoid users at two-year, 10-year and lifetime simulations, as shown in Table 4.5.2. Other options that follow are raloxifene therapy (RF) and HT-BP combination (HB) for two-year simulations, raloxifene therapy (RF) for 10-year simulations and calcitonin therapy (CN) for lifetime simulations. The patterns for 30-year-old and 50-year-old female glucocorticoid users are similar.

Table 4.5.2 Long-term estimates of cost-effectiveness for 50-year-old women

Length Treatment*	Cost§	Incremental Cost	Effectiveness	Incremental Effectiveness	C/E	ICER
2 years						
BP	$5,752	$5,207	0.9297	0.1760	$6,189	$29,586
CN	$4,495	$3,950	0.9804	0.2267	$4,585	$17,428
HB	$3,522	$2,977	0.9637	0.2100	$3,656	$14,179
HT	$1,049	$504	0.9863	0.2325	$1,064	$2,168
RF	$3,275	$2,730	0.9846	0.2308	$3,326	$11,825
CT	$545	reference	0.7538	reference	$726	-
10 years						
BP	$22,664	$19,696	0.8815	0.5518	$25,730	$35,692
CN	$17,167	$14,199	0.9390	0.6094	$18,285	$23,301
HB	$15,469	$12,501	0.9196	0.5900	$16,834	$21,188
HT	$6,356	$3,388	0.9249	0.5953	$6,880	$5,692
RF	$14,530	$11,562	0.9330	0.6033	$15,583	$19,165
CT	$2,968	reference	0.3297	reference	$9,222	-
Lifetime						
BP	$46,263	$40,412	0.4287	0.4106	$110,422	$98,418
CN	$37,090	$31,239	0.4657	0.4476	$80,976	$69,791
HB	$39,080	$33,228	0.3630	0.3449	$112,037	$96,333
HT	$27,282	$21,431	0.3439	0.3258	$82,435	$65,775
RF	$40,050	$34,199	0.3688	0.3507	$112,979	$97,519
CT	$5,851	reference	0.0181	reference	$427,670	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene group.

However, the pattern for 65-year-old female glucocorticoid users is different from previous cohorts with younger ages. Table 4.5.3 shows that, for 65-year-old female glucocorticoid users, the most cost-effective option remains hormone replacement therapy (HT) for two-year and 10-year simulations, and that calcitonin therapy (CN) dominates for lifetime simulations. Other options that follow are HT-BP combination (HB) in two-year, 10-year and lifetime simulations.

Table 4.5.3 Long-term estimates of cost-effectiveness for 65-year-old women

Length Treatment*	Cost§	Incremental Cost	Effectiveness	Incremental Effectiveness	C/E	ICER
2 years						
BP	$6,346	$5,649	0.9125	0.1578	$6,959	$35,789
CN	$4,602	$3,905	0.9685	0.2138	$4,753	$18,262
HB	$2,890	$2,193	0.9785	0.2239	$2,954	$9,793
HT	$2,004	$1,306	0.9561	0.2015	$2,097	$6,483
RF	$4,437	$3,739	0.9548	0.2002	$4,648	$18,681
CT	$697	reference	0.7546	reference	$928	-
10 years						
BP	$21,165	$17,315	0.8614	0.5024	$24,598	$34,462
CN	$17,563	$13,713	0.8873	0.5283	$19,806	$25,957
HB	$15,927	$12,077	0.8979	0.5389	$17,757	$22,411
HT	$13,523	$9,673	0.8107	0.4518	$16,760	$21,412
RF	$20,240	$16,390	0.8335	0.4745	$24,335	$34,538
CT	$3,850	reference	0.3590	reference	$10,919	-
Lifetime						
BP	$39,643	$32,672	0.4557	0.3846	$88,790	$84,942
CN	$33,345	$26,375	0.5414	0.4702	$62,257	$56,087
HB	$35,832	$28,861	0.5099	0.4388	$71,696	$65,775
HT	$32,502	$25,532	0.3829	0.3117	$87,733	$81,899
RF	$41,236	$34,266	0.4199	0.3488	$100,920	$98,237
CT	$6,971	reference	0.0711	reference	$109,810	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene group.

Table 4.5.4, Table 4.5.5 and Table 4.5.6 show estimates of long-term costs and effectiveness for male glucocorticoid users in hypothetical cohorts at different ages. The patterns in all tables are similar. Calcitonin therapy (CN) is the most cost-effective option for all cohorts in either two-year, 10-year or lifetime simulations.

Table 4.5.4 Long-term estimates of cost-effectiveness for 30-year-old men

Length Treatment*	**Cost§**	**Incremental Cost**	**Effectiveness**	**Incremental Effectiveness**	**C/E**	**ICER**
2 years						
BP	$3,686	$3,237	0.9582	0.0108	$3,848	$298,343
CN	$2,722	$2,272	0.9696	0.0223	$2,807	$102,114
CT	$449	reference	0.9473	reference	$475	-
10 years						
BP	$14,030	$11,760	0.7645	0.0527	$18,372	$222,999
CN	$12,620	$10,350	0.8452	0.1335	$14,952	$77,533
CT	$2,270	reference	0.7117	reference	$3,208	-
Lifetime						
BP	$23,855	$19,731	0.0058	-0.0161	$4,959,694	Dominated
CN	$28,737	$24,612	0.1985	0.1766	$149,122	$139,326
CT	$4,125	reference	0.0218	reference	$240,886	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

Table 4.5.5 Long-term estimates of cost-effectiveness for 50-year-old men

Length Treatment*	Cost§	Incremental Cost	Effectiveness	Incremental Effectiveness	C/E	ICER
2 years						
BP	$3,680	$3,001	0.9295	0.0116	$3,961	$259,485
CN	$2,908	$2,228	0.9537	0.0357	$3,050	$62,354
CT	$680	reference	0.9180	reference	$741	-
10 years						
BP	$13,130	$10,578	0.6436	0.0583	$20,452	$181,387
CN	$13,098	$10,546	0.7926	0.2073	$16,559	$50,873
CT	$2,552	reference	0.5853	reference	$4,403	-
Lifetime						
BP	$19,023	$15,323	0.0094	-0.0460	$2,374,513	Dominated
CN	$26,633	$22,932	0.2492	0.1937	$109,040	$118,364
CT	$3,700	reference	0.0554	reference	$76,637	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

Table 4.5.6 Long-term estimates of cost-effectiveness for 65-year-old men

Length of Treatment	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	C/E	ICER
2 years						
BP	$3,754	$3,091	0.8612	-0.0382	$4,362	Dominated
CN	$3,001	$2,338	0.9269	0.0275	$3,240	$85,082
CT	$663	reference	0.8994	reference	$738	-
10 years						
BP	$10,985	$8,803	0.3604	-0.1991	$30,872	Dominated
CN	$13,096	$10,914	0.6461	0.0866	$20,344	$126,052
CT	$2,182	reference	0.5595	reference	$3,940	-
Lifetime						
BP	$13,281	$10,226	0.0140	-0.1192	$1,107,952	Dominated
CN	$22,712	$19,658	0.2929	0.1596	$78,743	$123,191
CT	$3,055	reference	0.1333	reference	$24,579	-

Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures;
C/E=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.
§Costs are adjusted to 2005 dollars based on 5% annual discount rate.
*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

Figures 4.5.1 to 4.5.6 illustrate comparisons of cost-effectiveness among different treatment options with the same length of simulations based on information listed in Tables 4.5.1 to 4.5.6. Specifically, Figure 4.5.1 shows cost-effectiveness plots of base cases with two-year simulations for female glucocorticoid users. In female glucocorticoid users with a two-year period of treatments, hormone replacement therapy (HT) is the most cost-effective option at ages of 30, 50 and 65 years old, and bisphosphonate (BP) therapy is dominated by all treatments. The second recommended option for female glucocorticoid users is raloxifene (RF) for the 30-year-old cohort or HT-BP combination (HB) for the 65-year-old cohort.

Figure 4.5.2 shows cost-effectiveness plots of base cases with two-year simulations for male glucocorticoid users. In male glucocorticoid users with a two-year period of treatments, bisphosphonate (BP) therapy is dominated by calcitonin (CN) therapy at ages of 30, 50 and 65 years old. However, two-year BP therapy has a worse effectiveness than the control treatment (CT).

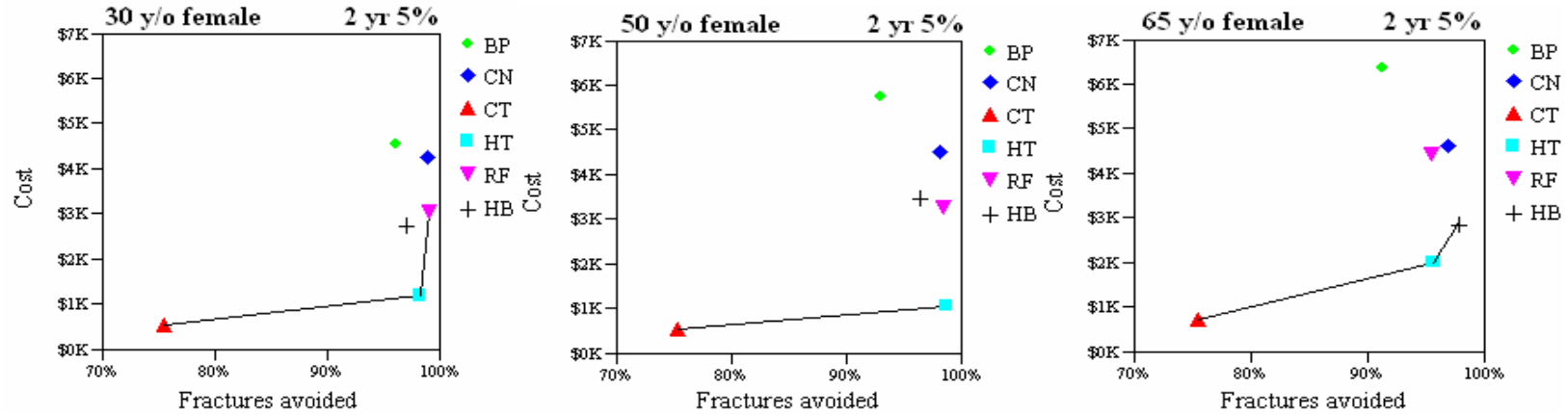


Figure 4.5.1 Costs and fractures avoided for female cohorts at different ages from 2-year estimations of base cases

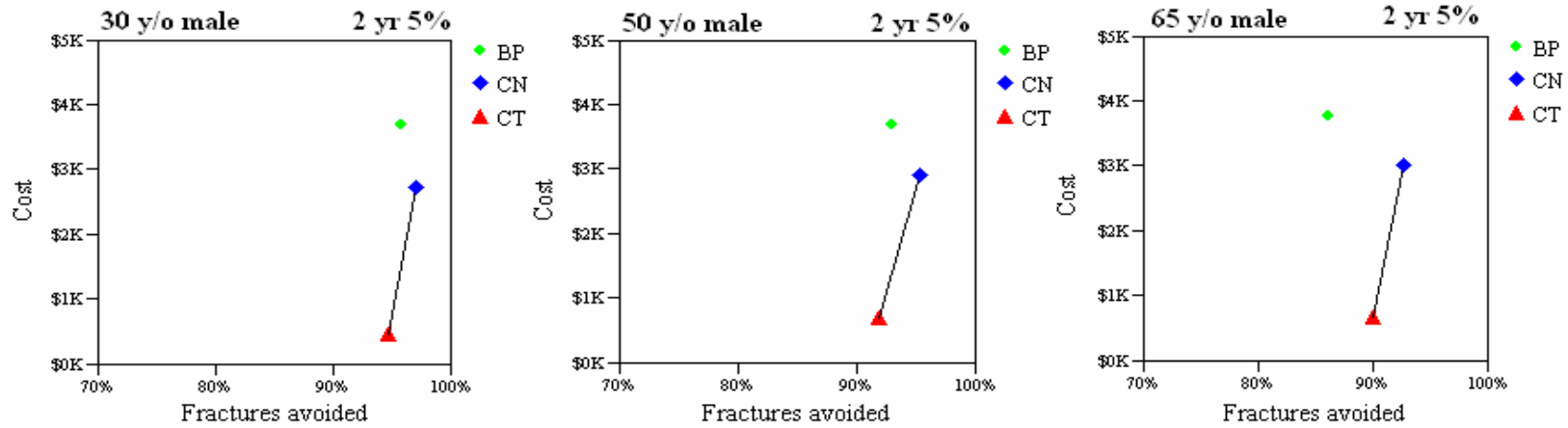


Figure 4.5.2 Costs and fractures avoided for male cohorts at different ages from 2-year estimations of base cases

Figure 4.5.3 shows cost-effectiveness plots of base cases with 10-year simulations for female glucocorticoid users. In female glucocorticoid users with a 10-year period of treatments, hormone replacement therapy (HT) is still the most cost-effective option at ages of 30, 50 and 65 years old. The second recommended option for female glucocorticoid users remains raloxifene (RF) for the 30-year-old cohort or HT-BP combination (HB) for the 65-year-old cohort. HB therapy is the second worse option for the 30-year-old cohort. Bisphosphonate (BP) therapy is dominated by most of the rest options. The patterns for recommended options for female glucocorticoid users for the two-year and 10-year simulations are similar.

Figure 4.5.4 shows cost-effectiveness plots of base cases with 10-year simulations for male glucocorticoid users. In male glucocorticoid users with a 10-year period of treatments, bisphosphonate (BP) therapy is dominated by calcitonin (CN) therapy at ages of 30, 50 and 65 years old. 10-year BP therapy has a worse effectiveness than the control treatment (CT); the patterns for male glucocorticoid users for the two-year and 10-year simulations are similar.

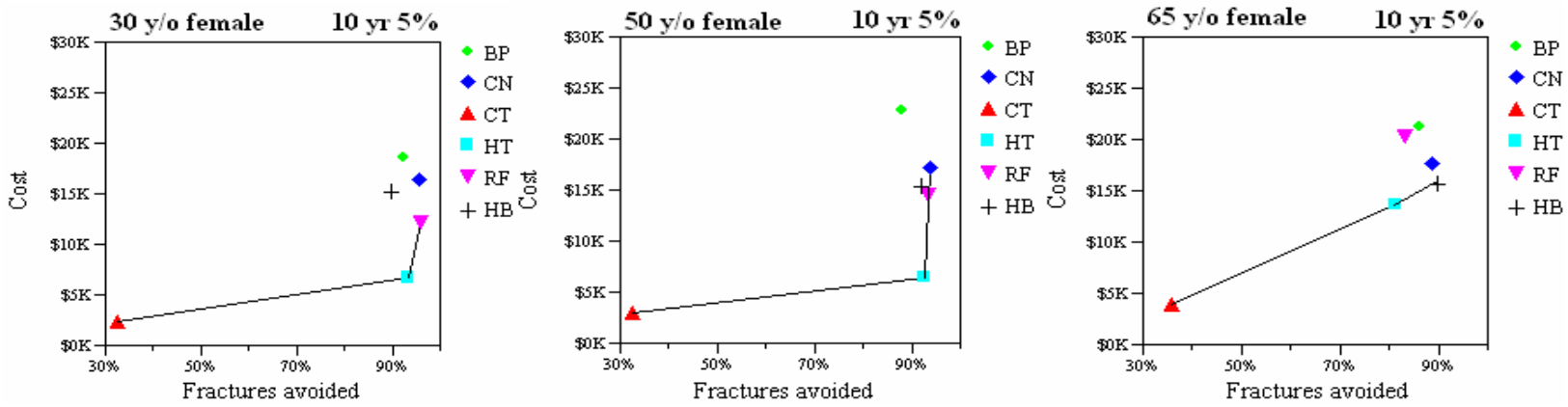


Figure 4.5.3 Costs and fractures avoided for female cohorts at different ages from 10-year estimations of base cases

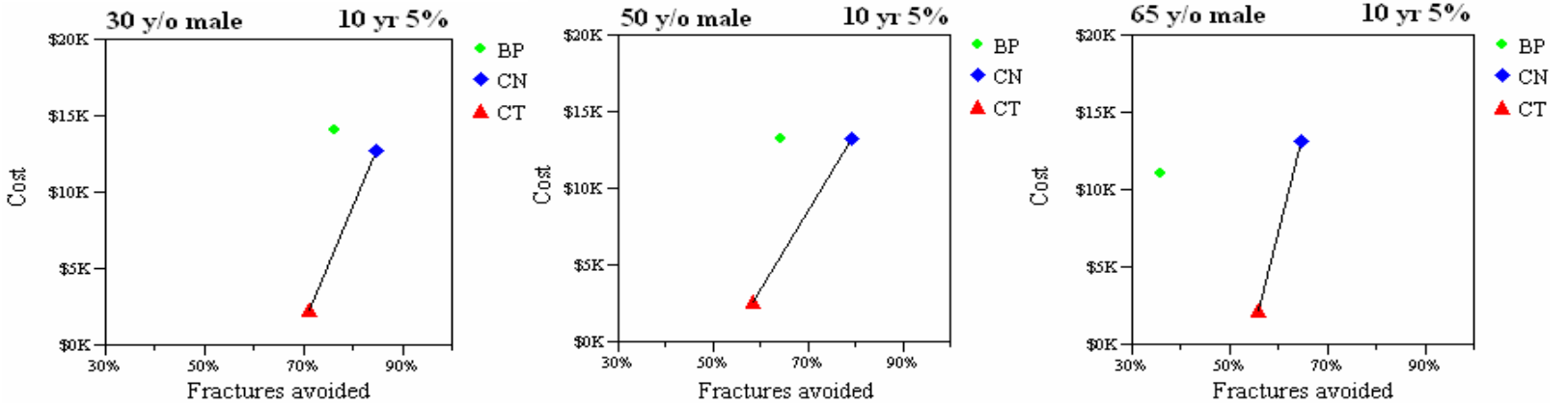


Figure 4.5.4 Costs and fractures avoided for male cohorts at different ages from 10-year estimations of base cases

Figure 4.5.5 shows cost-effectiveness plots of base cases with lifetime simulations for female glucocorticoid users. In female glucocorticoid users with lifetime estimates, hormone replacement therapy (HT) and calcitonin therapy (CN) are the most cost-effective options at ages of 30 and 50, but only CN therapy remains most cost-effective at 65 years of age. The HRT-BP combination (HB) is dominated by other treatments for the 30-year-old cohort, but is the next recommended option for the 65-year-old cohort.

Figure 4.5.6 shows cost-effectiveness plots of base cases with lifetime simulations for male glucocorticoid users. In male glucocorticoid users with lifetime estimates, bisphosphonate (BP) therapy is dominated by calcitonin (CN) therapy at ages of 30, 50 and 65 years old. Actually, BP therapy has the worse lifetime effectiveness in male glucocorticoid users than the control treatment (CT).

Based on the above analyses of base cases, the following options are recommended. For two-year and 10-year treatments, hormone replacement therapy (HT) works better for women at younger ages, followed by raloxifene therapy (RF); while HB treatment works better for women at age of 65 years old. For lifetime use of anti-osteoporotic treatment in female glucocorticoid users, calcitonin (CN) is the choice for women at any age, and hormone replacement therapy (HT) works better for women at younger ages. Bisphosphonate treatment (BP) is the least-favored option for most cases. In male glucocorticoid users, calcitonin therapy (CN) is superior to bisphosphonate (BP) and control treatments (CT) for any length of treatments and at any age. Nonetheless, the base-case analyses do not address uncertainty of model inputs, and the average estimates may not apply to all individuals. Therefore, sensitivity analyses were performed to check the robustness of the recommendations based on the base-case analyses.

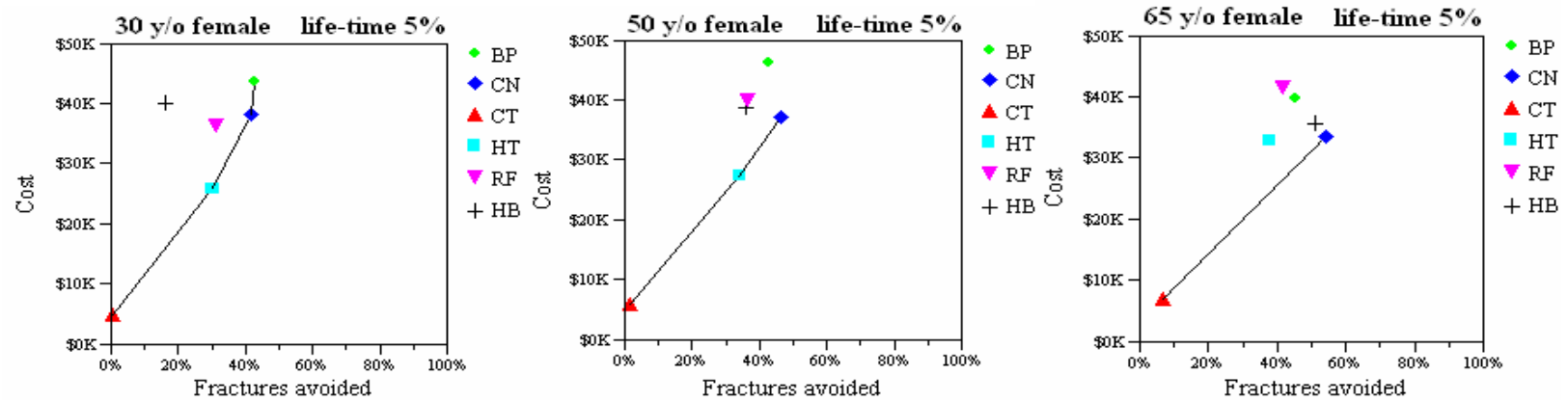


Figure 4.5.5 Costs and fractures avoided for female cohorts at different ages from lifetime estimations of base cases

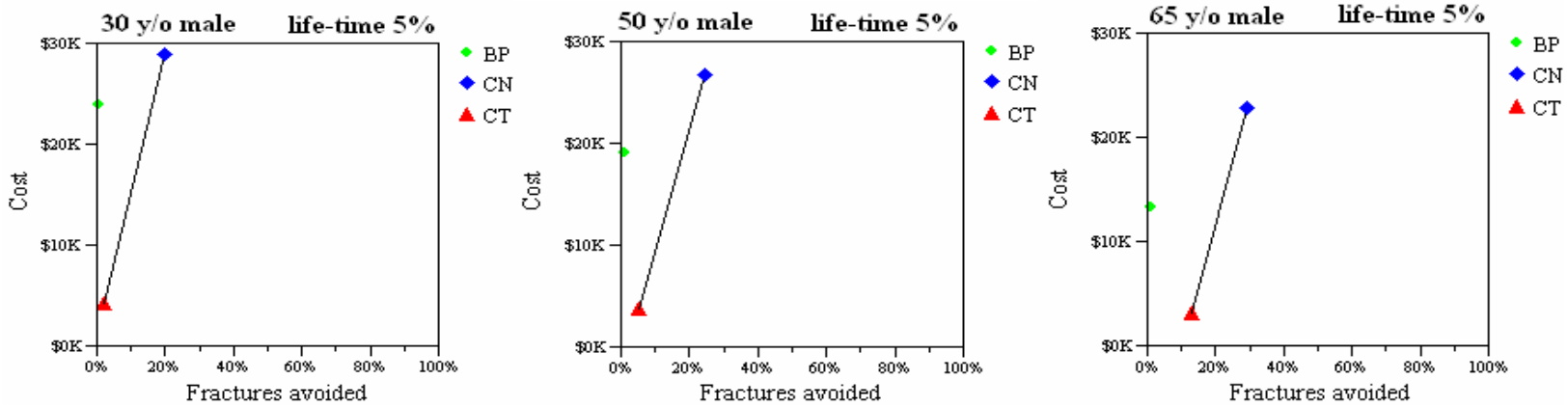


Figure 4.5.6 Costs and fractures avoided for male cohorts at different ages from lifetime estimations of base cases

4.5.2 Sensitivity Analyses

The analyses of base cases are based on most likely scenarios of costs and fracture rates; however, these estimates bear a certain degree of uncertainty. For example, the standard error of the average costs of the first-time fractures ($4,832) among HRGS users is $924.9. A few transition probabilities are derived based on indirect sources and logistic regression models. The "variable" uncertainty from these estimates may have a significant impact on long-term estimates of outcomes in the modeling. Traditional one-way or two-way sensitivity analyses cannot address the uncertainty of these model inputs simultaneously. A second-order Monte-Carlo simulation serves as a tool to address uncertainties at the level of variables simultaneously, so it was performed for each Markov model cohort.

4.5.2.1 Monte Carlo Simulations

In each hypothetical cohort, a total of 10,000 samples were simulated by second-order Monte Carlo simulations based on a set of transition probabilities and costs with variance introduced. The variance was assigned based on proper statistical distributions which account for hypothetical measurement error by chance. Figure 4.5.7 illustrates the results of costs and effectiveness drawn from 1,000 of 10,000 samples in each female cohort; results are presented by different ages and lengths of treatment periods. Among female cohorts, with an increased age or increased lengths of treatment, the best or better option among treatments is less clear. Additional sensitivity analysis is required for female glucocorticoid users to further facilitate the decision-making processes.

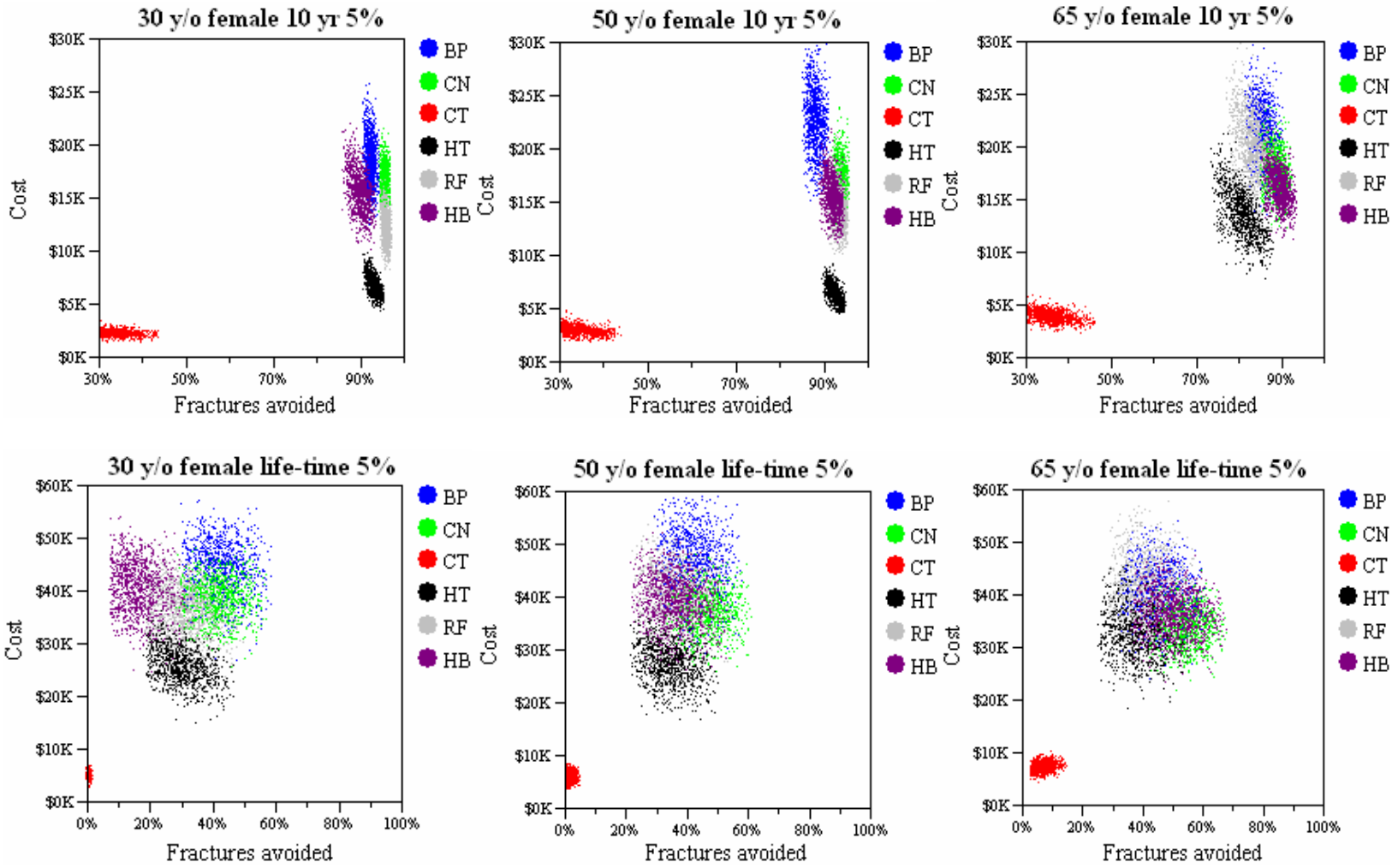


Figure 4.5.7 Monte Carlo simulations on variable uncertainty for female cohorts

Figure 4.5.8 illustrates the results of cost and effectiveness, drawn from 1,000 of 10,000 samples in each male cohort; results are presented by different ages and lengths of treatment periods. The decisions should be relatively clear for male glucocorticoid users. Therefore, no further sensitivity analysis is performed for male glucocorticoid users.

4.5.2.2 Annual Discount Rates

The variety of annual discount rates is not included in the Monte-Carlo simulations, so a separate sensitivity analysis was performed to check the robustness of recommendations. The analyses of base cases used an annual discount rate of 5%; another analysis was performed by using annual discount rate of 3%. A cohort of 50-year-old female glucocorticoid users was used as an example.

Table 4.5.7 shows estimates of long-term costs and effectiveness for 50-year-old female glucocorticoid users based on the annual discount rate of 3% (see Table 4.5.2 for the estimates using the rate of 5%). The estimates of effectiveness between these two tables are identical. Figures 4.5.9 illustrates cost-effectiveness plots based on Table 4.4.5 and Table 4.5.1. For the two-year simulation, the difference in estimates is subtle because of the short period of time. The patterns among treatments are similar between estimates from annual discount rate of either 3% or 5%. Therefore, the recommendations for 50-year-old female glucocorticoid users are robust between annual discount rates of 3% and 5%. A similar pattern was found between annual discount rates of 3% and 5% within the same cohort. Data and figures are not shown. It suggests that annual discount rates have a minimal impact on recommendations.

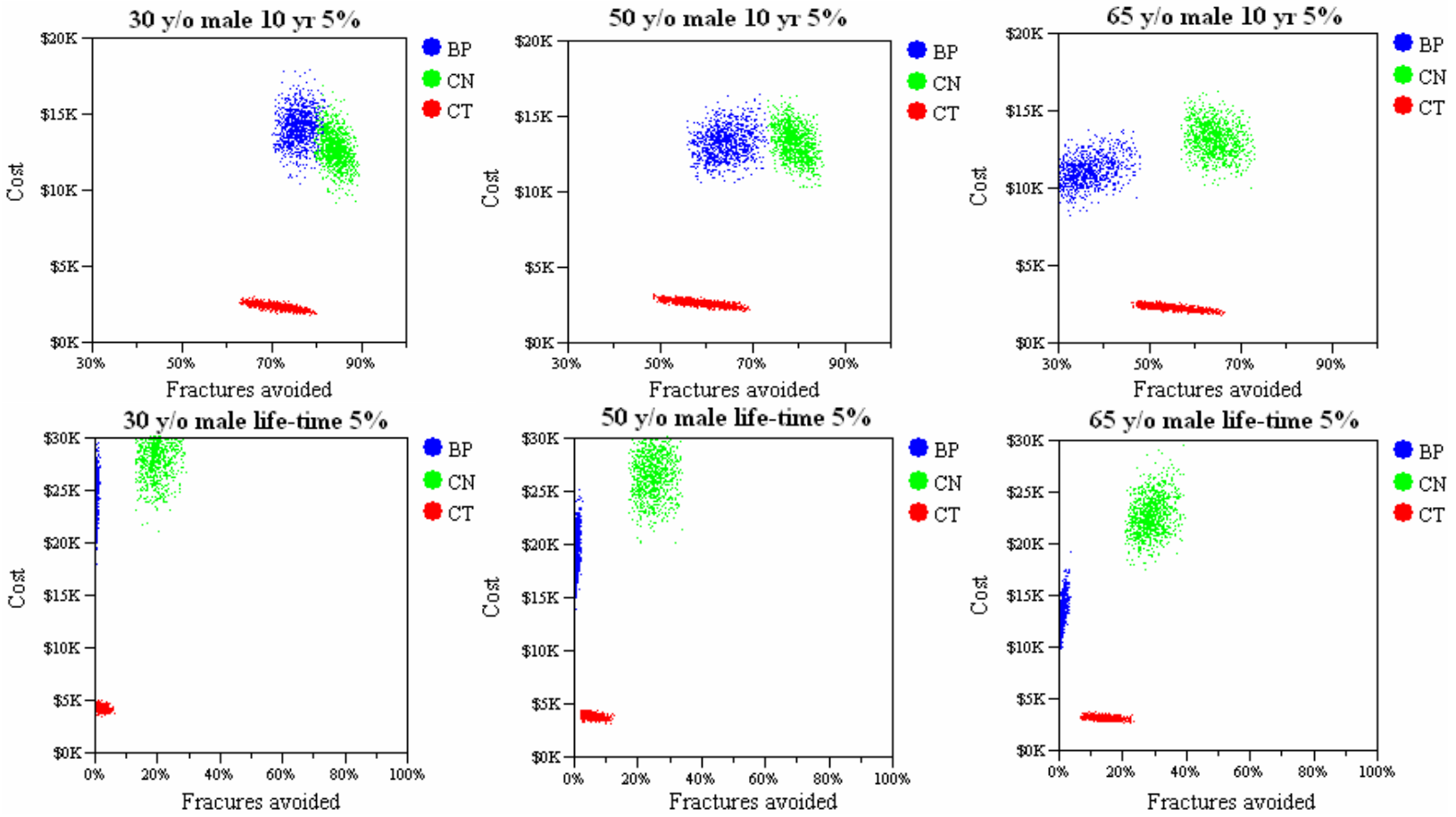


Figure 4.5.8 Monte Carlo simulations on variable uncertainty for male cohorts

Table 4.5.7 Estimates of long-term costs and effectiveness for 50-year-old women, annual discount rate 3%

Length Treatment*	Cost§	Incremental Cost	Effectiveness†	Incremental Effectiveness	C/E	Incremental C/E
2 years						
BP	5,840	$5,287	0.9297	0.1759	$4,730	$30,057
CN	4,568	$4,015	0.9804	0.2266	$4,298	$17,718
HB	1,066	$513	0.9637	0.2099	$2,869	$2,444
HT	3,326	$2,773	0.9863	0.2325	$1,210	$11,927
RF	3,577	$3,024	0.9846	0.2308	$3,077	$13,102
CT	553	reference	0.7538	reference	$711	-
10 years						
BP	24,868	$21,580	0.8815	0.5518	$20,025	$39,108
CN	18,830	$15,542	0.9390	0.6093	$16,984	$25,508
HB	7,076	$3,788	0.9196	0.5899	$17,205	$6,421
HT	16,027	$12,739	0.9249	0.5952	$7,137	$21,403
RF	17,037	$13,749	0.9330	0.6033	$12,622	$22,790
CT	3,288	reference	0.3297	reference	$6,924	-
Lifetime						
BP	62,390	$54,875	0.4287	0.4106	$103,516	$133,646
CN	50,573	$43,058	0.4657	0.4476	$93,384	$96,197
HB	41,231	$33,716	0.3630	0.3449	$267,380	$97,756
HT	57,078	$49,563	0.3439	0.3258	$88,629	$152,127
RF	55,022	$47,507	0.3688	0.3507	$121,283	$135,463
CT	7,515	reference	0.0181	reference	$1,416,526	-

§Costs are adjusted to 2005 dollars based on 3% annual discount rate.

†Effectiveness: 1=no osteoporotic fractures at all; 0=100% chance of osteoporotic fractures.

*BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; Index=average age multiplied by four; RF=raloxifene group.

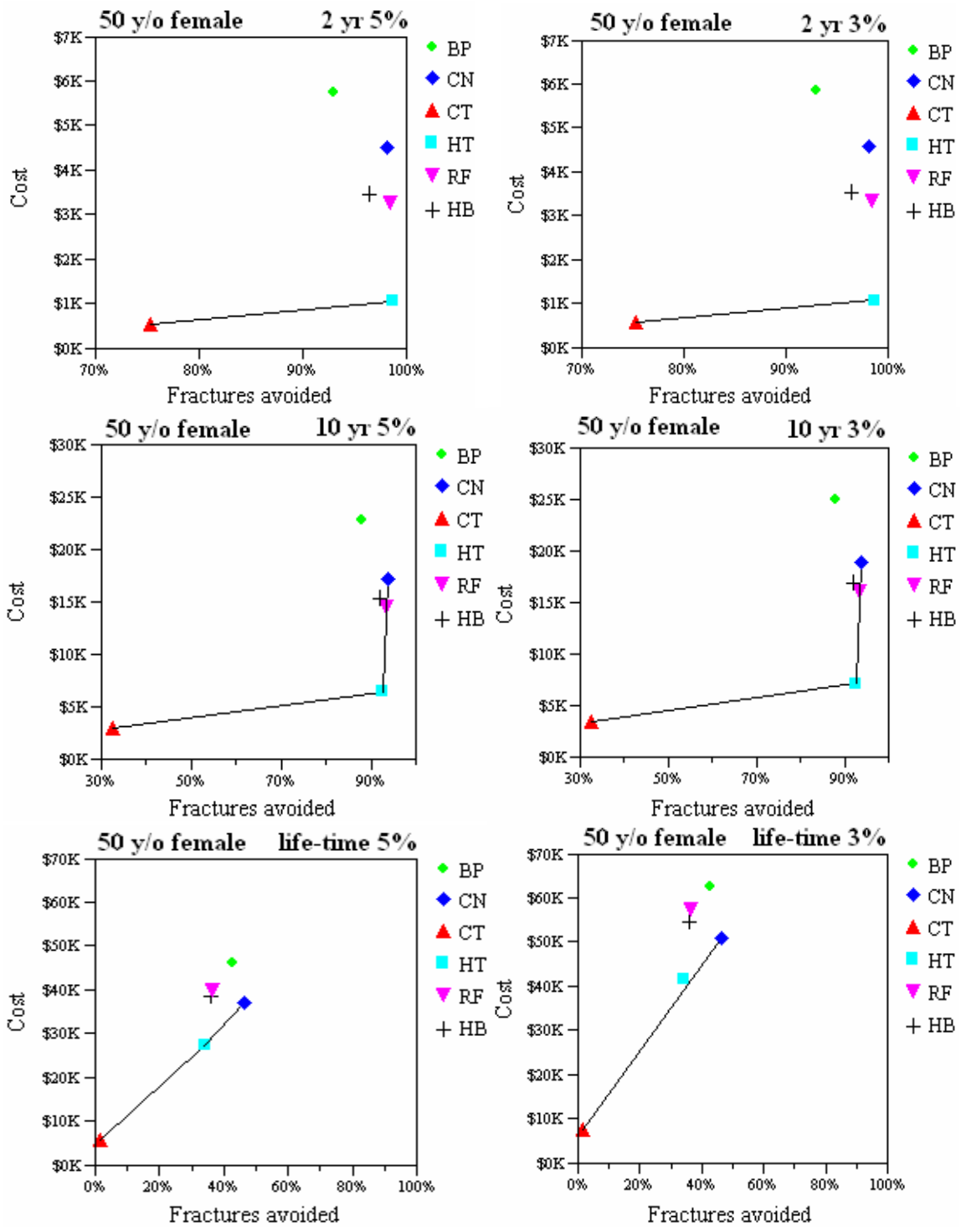
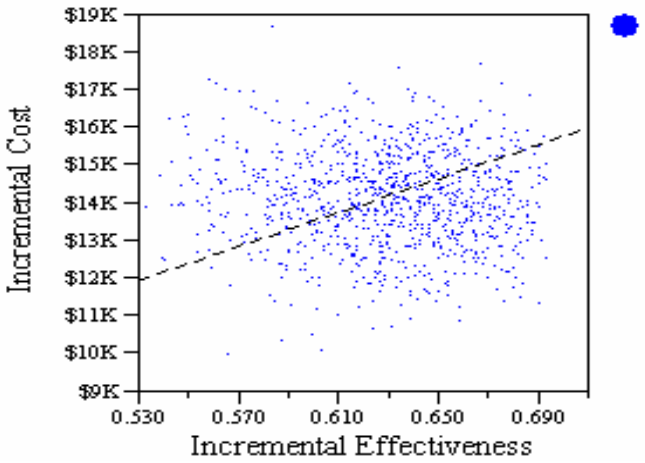


Figure 4.5.9 Costs and fractures avoided for 50-year-old female glucocorticoid users at different annual discount rates

4.5.2.3 Willingness-To-Pay

Compared to the baseline option (i.e., The CT group for this study), second-order Monte Carlo simulations also yield information on probabilities of cost-effective samples for a treatment based on a threshold incremental cost-effectiveness ratio (ICER), which usually equals the willingness-to-pay (WTP) value. Figure 4.5.10 shows the scatterplot of incremental cost and effectiveness in 1,000 of 10,000 samples in simulations for 30-year-old female glucocorticoid users who use 10-year calcitonin treatment when it is compared to control group. A ceiling ratio of $22,500 was developed to establish a break-even point; it was not a pre-established WTP value. The control group (baseline option) is on the origin so it is not visible in the Figure. Samples below the dashed line, which represents WTP, are cost-effective. This scatterplot indicates that if a 30-year-old female glucocorticoid user is willing to pay a total of $22,500 more for a 10-year calcitonin treatment in addition to a strategy of "screening for osteoporosis" (control treatment), the probability to reach cost-effective results is 52.65%.



----dashed line indicates WTP=$22,500
*1,000 points of 10,000 subjects shown

Figure 4.5.10 Scatterplot of incremental cost and effectiveness for 30-year-old female glucocorticoid users with 10-year calcitonin treatment compared to control group

The same analysis was performed for 30-year-old female glucocorticoid users who want to pay 10-year calcitonin treatment at different amounts of WTP. Table 4.5.8 shows percentages of cost-effective samples of 30-year-old female glucocorticoid users for a 10-year calcitonin treatment based on different WTP values. Based on information shown in Table 4.5.8, Figure 4.5.11 illustrates the acceptability curve of calcitonin treatment for 30-year-old female glucocorticoid users by different WTP values.

Table 4.5.8 Percentages of cost-effective samples of 30-year-old female glucocorticoid users for a 10-year calcitonin treatment by WTP

Willingness-to-pay (*$1,000)	15.0	17.5	20.0	22.5	25.0	27.5	30.0	32.5
% Cost-effective	0.0	7.1	15.7	52.7	86.4	97.4	99.7	100.0

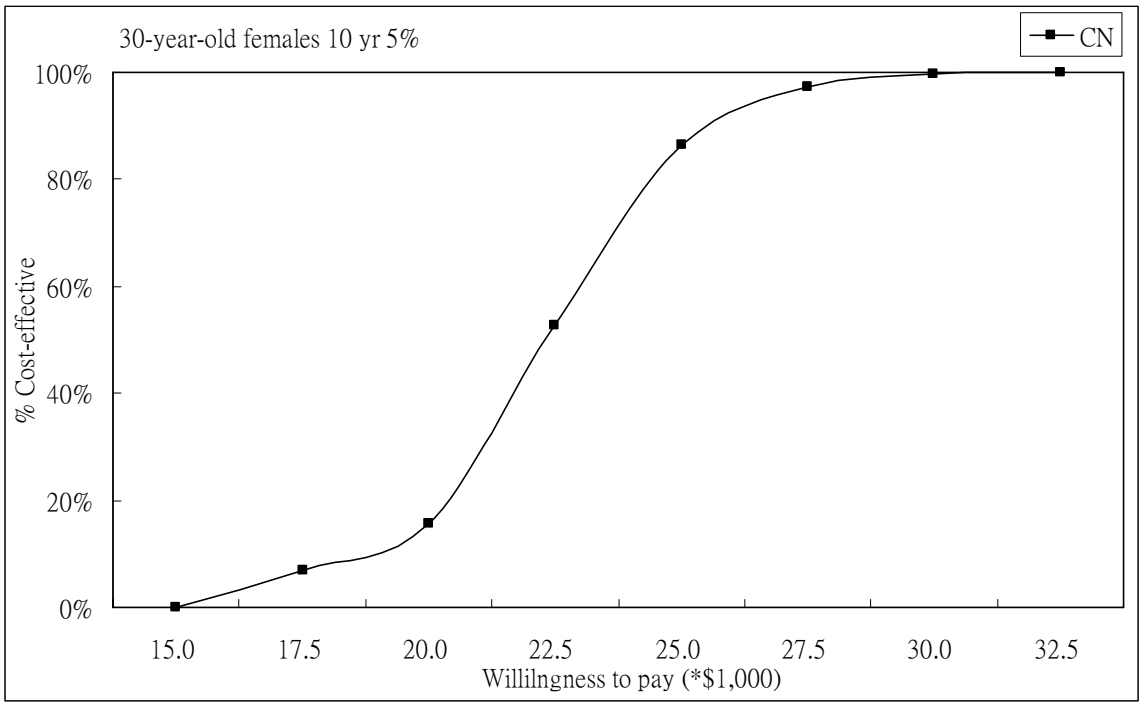


Figure 4.5.11 Acceptability curve of 10-year calcitonin treatment compared to control group in 30-year-old female glucocorticoid users

The same analysis was performed for all treatment options and by different values of WTP. Table 4.5.9 shows percentages of cost-effective samples of 30-year-old female glucocorticoid users for a 10-year treatment based on different WTP values. Based on information shown in Table 4.5.9, Figure 4.5.12 illustrates the acceptability curve of each treatment option by WTP values. In Figure 4.5.3, which was illustrated earlier, HT is the most cost-effective option, followed by RF. If a payer can afford $30,000 for a 10-year treatment to avoid an incidence of osteoporotic fracture, of HT, RF, CN or HB has almost a 100% probability of reaching the goal. If the payer can tolerate 20% failure in treatment, BP treatment may be one of the options, too. Decisions on the selection of treatments may also depend on WTP. Similarly, Figures 4.5.13 to 4.5.17 illustrate acceptability curves for female cohorts with different ages and length of treatment periods. The acceptability curve on the far left usually implies that treatment is the most cost-effective option for the cohort.

Table 4.5.9 Percentage of cost-effective samples by willingness to pay and treatment

WTP*	5.0	7.5	10.0	12.5	15.0	17.5	20.0	22.5	25.0	27.5	30.0	32.5	35.0	40.0
Treatment	**% cost-effective**													
BP							0.8	6.3	22.2	51.6	80.6	94.3	99.0	100.0
CN					0.0	7.1	15.7	52.7	86.4	97.4	99.7	100.0		
HB					0.0	0.9	9.2	39.2	77.3	96.4	99.7	100.0		
HT	0.0	61.1	100.0											
RF			0.0	3.2	34.0	85.3	98.7	100.0	100.0					

*WTP=willingness to pay in a unit of US $1,000.

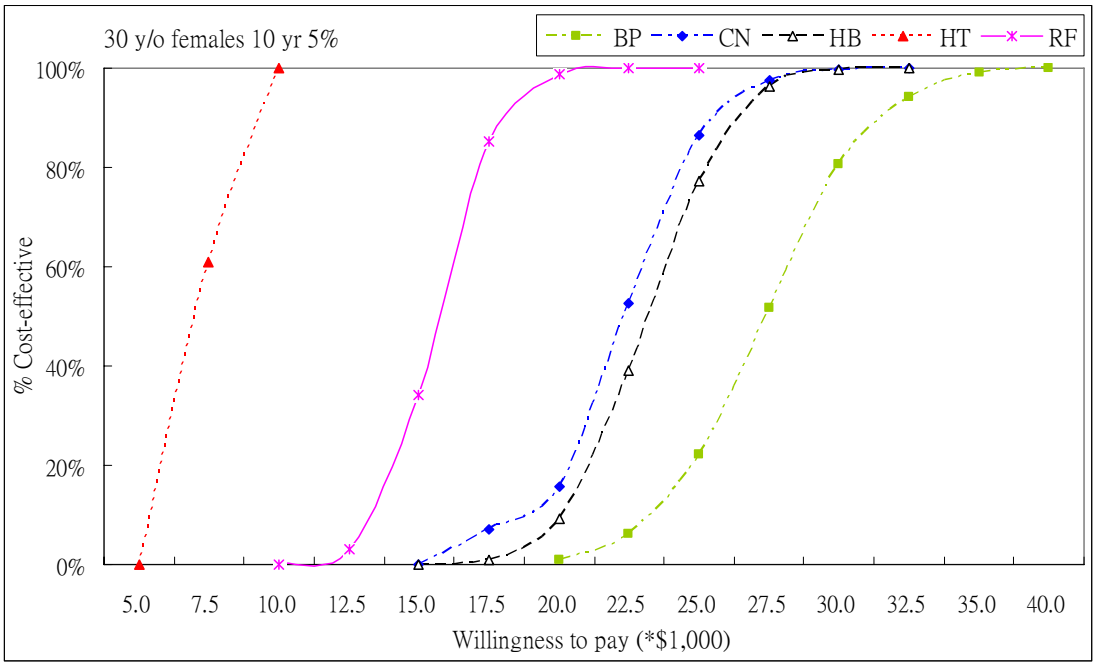


Figure 4.5.12 Acceptability curves of 10-year anti-osteoporotic treatments compared to control group in 30-year-old female glucocorticoid users

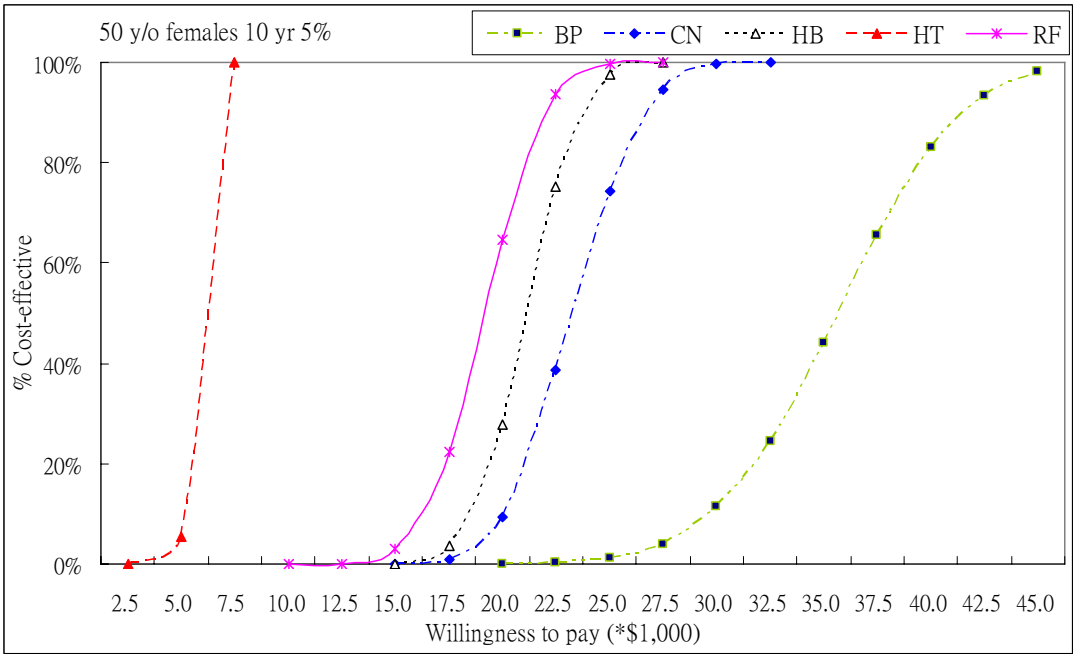


Figure 4.5.13 Acceptability curves of 10-year anti-osteoporotic treatments compared to control group in 50-year-old female glucocorticoid users

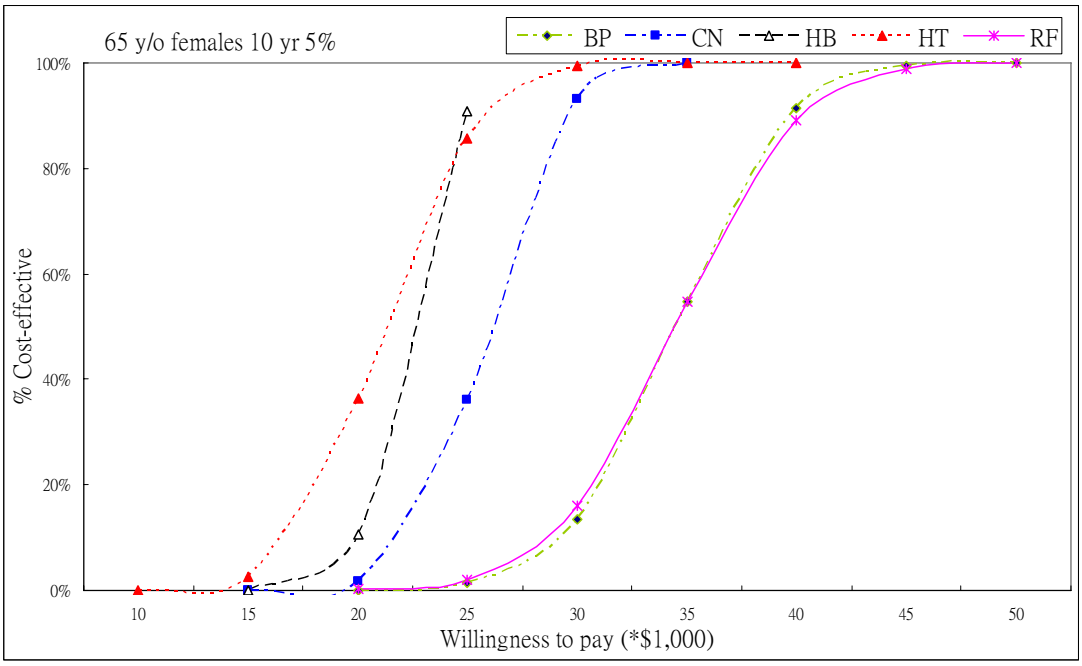


Figure 4.5.14 Acceptability curves of 10-year anti-osteoporotic treatments compared to control group in 65-year-old female glucocorticoid users

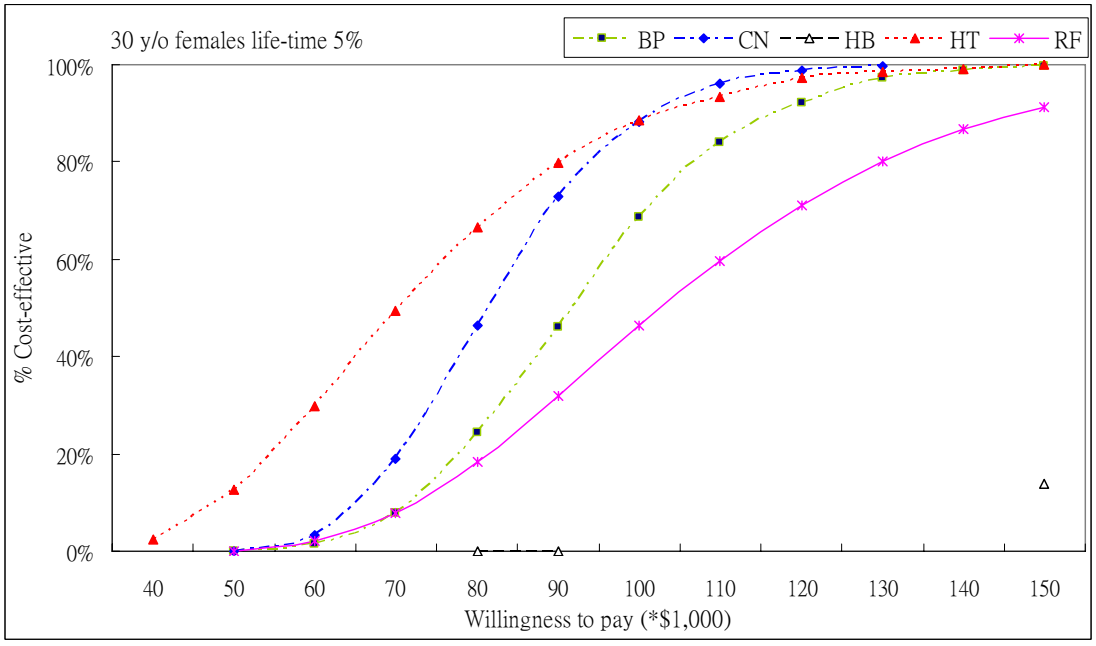


Figure 4.5.15 Acceptability curves of lifetime anti-osteoporotic treatments compared to control group in 30-year-old female glucocorticoid users

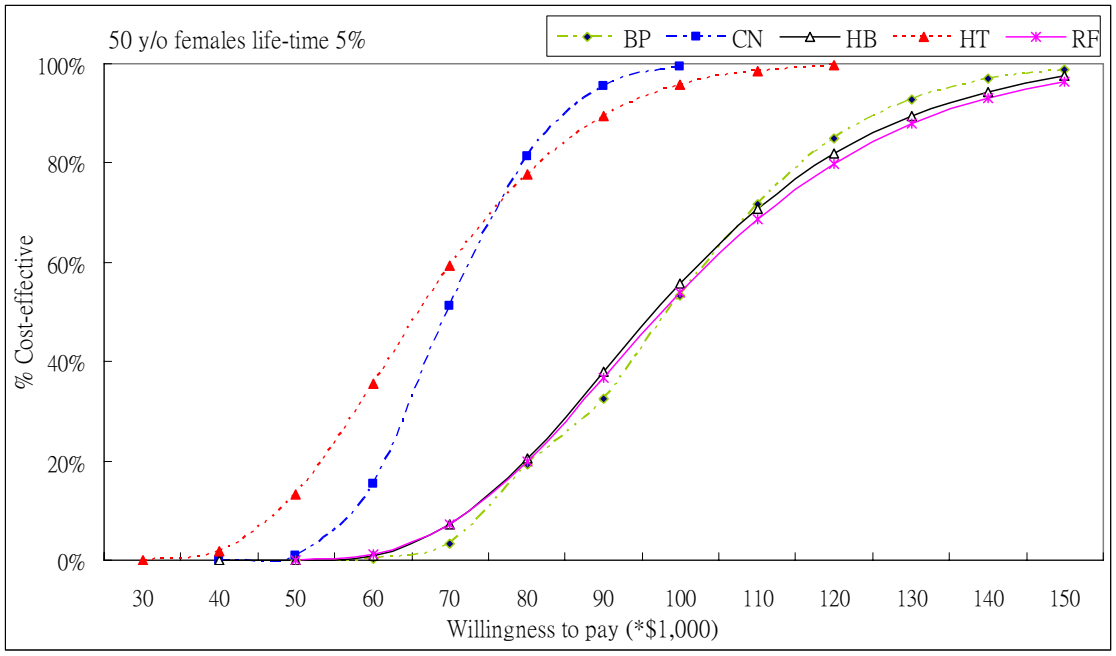


Figure 4.5.16 Acceptability curves of lifetime anti-osteoporotic treatments compared to control group in 50-year-old female glucocorticoid users

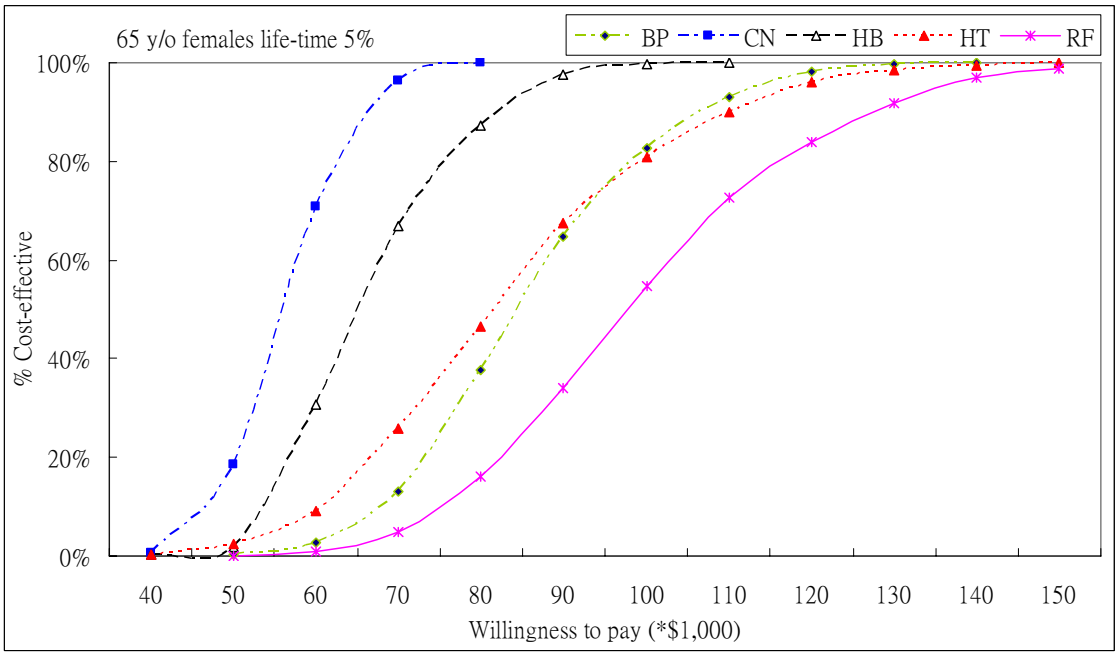


Figure 4.5.17 Acceptability curves of lifetime anti-osteoporotic treatments compared to control group in 65-year-old female glucocorticoid users

These figures may also serve as informal tests for the sixth study hypotheses by drawing a line on x-axls of WTP and checking whether the percentage of cost-effective for each treatment option reaches at least 95% (or any alpha level determined by the decision makers). The the ceiling costs (R_c) or WTP values were assumed as $1,000, $10,000 and $100,000 per fracture avoided (see Section 2.9.6). No treatment option is cost-effective based on a WTP of $1,000 per fracture avoided. Hormone replacement therapy is the most cost-effective option based on a WTP of $10,000 per fracture avoided. Most treatment options are accepted based on a WTP of $100,000 per fracture avoided. With regard to the selection of a preferred opton, the acceptability curves provide useful information which assists decision-making processes based on different needs.

The acceptability curves implied that there were significant differences in ICERs among different treatment groups. Therefore, all hypotheses for the sixth study objective were rejected. Table 4.5.10 summaries all study hypoetheses and results of hypothesis testing.

Table 4.5.10 Summary of study hypotheses and test results

	Description of hypothesis	Rejected or Not rejected
Average age		
Ho_{1A1}	There is no significant difference in average ages among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 172)
Ho_{1A2}	There is no significant difference in average ages among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 172)
Ho_{1A3}	There is no significant difference in average ages among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 172)
Ho_{1A4}	There is no significant difference in average ages among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 172)
Average cumulative glucocorticoid dose		
Ho_{1B1}	There is no significant difference in average cumulative glucocorticoid doses among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 172-173)
Ho_{1B2}	There is no significant difference in average cumulative glucocorticoid doses among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 172-173)
Ho_{1B3}	There is no significant difference in average cumulative glucocorticoid doses among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 172-173)
Ho_{1B4}	There is no significant difference in average cumulative glucocorticoid doses among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 172-173)
Average cumulative quantity of oral glucocorticoid tablets		
Ho_{1C1}	There is no significant difference in average cumulative quantity of oral glucocorticoid tablets among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 173-174)
Ho_{1C2}	There is no significant difference in average cumulative quantity of oral glucocorticoid tablets among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 173-174)
Ho_{1C3}	There is no significant difference in average cumulative quantity of oral glucocorticoid tablets among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 173-174)
Ho_{1C4}	There is no significant difference in average cumulative quantity of oral glucocorticoid tablets among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 173-174)

Table 4.5.10 Summary of study hypotheses and test results (continued)

	Description of hypothesis	Rejected or Not rejected
Average glucocorticoid dose per tablet		
Ho_{1D1}	There is no significant difference in average glucocorticoid dose per tablet among female long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 174)
Ho_{1D2}	There is no significant difference in average glucocorticoid dose per tablet among male long-term glucocorticoid users (LTGS) who received different anti-osteoporotic treatments.	Rejected (page 174)
Ho_{1D3}	There is no significant difference in average glucocorticoid dose per tablet among female high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 174)
Ho_{1D4}	There is no significant difference in average glucocorticoid dose per tablet among male high-risk glucocorticoid users (HRGS) who received different anti-osteoporotic treatments.	Rejected (page 174)
Average direct medical costs of preventive anti-osteoporotic treatments		
Ho_{4A1}	There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for female long-term glucocorticoid users (LTGS).	Rejected (page 206)
Ho_{4A2}	There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for male long-term glucocorticoid users (LTGS).	Rejected (page 206)
Ho_{4B1}	There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for female high-risk glucocorticoid users (HRGS).	Rejected (page 206)
Ho_{4B2}	There is no significant difference in average direct medical costs of preventive anti-osteoporotic treatments for male high-risk glucocorticoid users (HRGS).	Rejected (page 206)
Average long-term costs of anti-osteoporotic treatments		
Ho_{5A1}	There is no significant difference in average direct medical costs of 10-year anti-osteoporotic treatments for female glucocorticoid tablet users.	Rejected (page 217-8)
Ho_{5A2}	There is no significant difference in average direct medical costs of 10-year anti-osteoporotic treatments for male glucocorticoid tablet users.	Rejected (page 220)
Ho_{5B1}	There is no significant difference in average direct medical costs of lifetime anti-osteoporotic treatments for female glucocorticoid tablet users.	Rejected (page 217, 219)
Ho_{5B2}:	There is no significant difference in average direct medical costs of lifetime anti-osteoporotic treatments for male glucocorticoid tablet users.	Rejected (page 220)

Table 4.5.10 Summary of study hypotheses and test results (continued)

	Description of hypothesis	Rejected or Not rejected
Average long-term effectiveness of anti-osteoporotic treatments		
Ho_{5C1}	There is no significant difference in average effectiveness of 10-year anti-osteoporotic treatments for female glucocorticoid tablet users.	Rejected (page 218)
Ho_{5C2}	There is no significant difference in average effectiveness of 10-year anti-osteoporotic treatments for male glucocorticoid tablet users.	Rejected (page 220)
Ho_{5D1}	There is no significant difference in average effectiveness of lifetime anti-osteoporotic treatments for female glucocorticoid tablet users.	Rejected (page 217, 219)
Ho_{5D2}	There is no significant difference in average effectiveness of lifetime anti-osteoporotic treatments for male glucocorticoid tablet users.	Rejected (page 220)
Incremental long-term cost-effectiveness ratio (ICER)		
Ho_{6A1}	The incremental cost-effectiveness ratios (ICERs) of a 10-year anti-osteoporotic treatment for female glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, equals the ceiling cost (R_c).	Rejected (page 246)
Ho_{6A2}	The incremental cost-effectiveness ratios (ICERs) of a 10-year anti-osteoporotic treatment for male glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, equals the ceiling cost (R_c).	Rejected (page 246)
Ho_{6B1}	The incremental cost-effectiveness ratios (ICERs) of a lifetime anti-osteoporotic treatment for female glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, equals the ceiling cost (R_c).	Rejected (page 246)
Ho_{6B2}	The incremental cost-effectiveness ratios (ICERs) of a lifetime anti-osteoporotic treatment for male glucocorticoid tablet users, compared to those who do not use any anti-osteoporotic agent, equals the ceiling cost (R_c).	Rejected (page 246)

4.6 SUMMARY OF CHAPTER FOUR

In combined data from the 1996 to 2004 Medical Expenditure Panel Survey (MEPS), an average number of 30,235 subjects per year represent an estimated average of 280,566,064 non-institutionalized people in the U.S. Of these MEPS subjects, the weighted average age is 35.6 years old [Standard error of the mean (SE) =0.16], 52.3% are female, 81.7% are white and 12.8% are black or Africa American. Study results for high-risk glucocorticoid (HRGS) users are similar to those for long-term glucocorticoid (LTGS) users, so results for LTGS users were summarized for simplicity.

A total of 5,461 subjects met the study criteria for long-term glucocorticoid users (LTGS). Overall, 2.2% of non-institutionalized U.S. population are LTGS users (1.8% of males and 2.7% of females). Of these LTGS users, the weighted average age is 49.7 years old (SE=0.53); 61.4% are female, 86.2% are white, 10.0% are black or African American, the average length of glucocorticoid therapy is 237.2 days (weighted, SE=8.93 days) and the weighted average daily dose (prednisone equivalent) is 11.0 mg (SE=0.17 mg). In LTGS users, at least 25.3% of glucocorticoid prescriptions were prescribed for respiratory diseases, followed by joint problems (21.9%).

Overall, 12.0% of MEPS subjects or 22.4% of LTGS users reported use of any anti-osteoporotic agent. The most frequently used type among all anti-osteoporotic agents is hormone replacement therapy (HT) in women or use of both bisphosphonates and calcitonin for men. The next most frequently used type is bisphosphonates. Analysis of variance (ANOVA) indicates that LTGS users in the control and the HT groups are significantly younger (df=5, F=36.17, $p<0.0001$) than those in other treatment groups. ANOVA also indicates that the control group in LTGS users has a lower average cumulative glucocorticoid dose ($p=0.0122$). The majority of LTGS users in

each treatment group is white (77.6% to 100.0%). The differences in background of LTGS users among different treatment groups may imply a selection bias.

LTGS users had higher prevalence rates of osteoporosis and osteoporotic fractures than the general population in the U.S. Women had higher prevalence rates of osteoporosis than men in both groups, but the prevalence rates of osteoporotic fractures were similar. From 1996 to 2004, it is estimated that the average annual prevalence of osteoporosis is 1,646 per 1,000,000 person-years (PY) for men, 23,355 per 1,000,000 PY for women, 9,768 per 1,000,000 PY for male LTGS users and 67,572 per 1,000,000 PY for female LTGS users in the U.S. During the same period of time, it is also estimated that that the estimated average annual prevalence of osteoporotic fractures is 18,488 per 1,000,000 PY for men, 17,995 per 1,000,000 PY for women, 29,764 per 1,000,000 PY for male LTGS users and 29,971 per 1,000,000 PY for female LTGS users in the U.S.

The incidence rates of osteoporosis and osteoporotic fractures differ by gender, age, prior exposure to osteoporosis or fractures, type of glucocorticoid use and type of treatment received. In general, incidence rates of osteoporosis in female glucocorticoid users are higher than those rates in MEPS female subjects, and those rates in groups of older age groups are likely larger than those in younger groups; however, it is not absolute. A similar trend was not observed for incidence rates of osteoporotic fractures. In some cases, subjects in the 51 to 70 year-old age groups had relatively higher incidence rates of osteoporotic fractures. It appears that the patterns are inconsistent. The logistic regression analyses indicated that the use of oral glucocorticoid tablets does not significantly change the odds of osteoporotic fractures in study subjects (relative risk (RR)= 1.146, 95% confidence interval (CI) 0.901-1.458 for subjects in the WELL state; RR=0.55, 95% CI 0.188-1.621 for subjects in the GIOP state; RR=1.241, 95% CI 0.532-2.893 for subjects in GIFX state).

It is estimated that the average direct medical cost for evaluation of osteoporosis is $347.9 (SE=$24.3, 2005 dollars) per three months in LTGS users. The average direct medical costs for osteoporotic fractures in LTGS users are $4,933 (SE=$443, 2005 dollars) for first-time osteoporotic fractures and $6,710 for repeated osteoporotic fractures. For LTGS users, the average total direct medical costs of anti-osteoporotic treatments for two years are $850 (SE=$44.1) for bisphosphonate therapy, $882.4 (SE=$81.7) for calcitonin therapy, $631 (SE=$59.4) for hormone replacement therapy, $875.5 (SE=$31.1) for combined use of hormone-replacement and bisphosphonate therapy and $963.9 (SE=114) for raloxifene therapy.

Long-term estimates of costs and effectiveness were generated for hypothetical male and female cohorts with different ages in each group of anti-osteoporotic treatments by using Markov modeling and Monte Carlo simulations. Analyses of long-term costs and effectiveness among treatment groups indicate that the 30-year-old and 50-year-old female cohorts have a similar pattern of comparisons, while the pattern for the 65-year-old female cohorts is different. Comparisons of acceptability curves of different anti-osteoporotic treatments indicate that hormone replacement therapy is the most cost-effective option for hypothetical female cohorts for either two-year, 10-year or lifetime estimations except that calcitonin therapy is the most cost-effective option for 65-year-old female cohorts for lifetime estimations. The cost-effectiveness patterns among bisphosphonate, calcitonin and control groups for hypothetical male cohorts are similar. Calcitonin therapy is the most cost-effective option for hypothetical male cohorts at any age and any length of simulations. One-way sensitivity analysis on annual discount rates indicates the patterns of study results are robust in comparisons among different groups of anti-osteoporotic treatments.

CHAPTER FIVE-DISCUSSION AND CONCLUSIONS

This chapter interprets and discusses the study results, and provides recommendations for treatment of glucocorticoid-induced osteoporosis and fractures. The first section discusses important study findings and compares some of these findings to those from other studies in the literature. The next section discusses study limitations. The third section brings up some possible topics for future research. The last section makes recommendations for the management of glucocorticoid-induced osteoporosis and related fractures.

5.1 DISCUSSION

There have been a few studies investigating the cost-effectiveness of anti-osteoporotic treatments for osteoporosis, especially for post-menopausal osteoporosis in the literature. Little has been published about the long-term cost-effectiveness of anti-osteoporotic treatments for glucocorticoid-induced osteoporosis. This section compares the study findings to what was found in the literature.

5.1.1 Study Subjects

Previous studies estimated that about 0.7% of the general population in Iceland are long-term glucocorticoid (LTGS) users, and 0.9% of the general population in the

U.K. had received oral glucocorticoid therapy.[305, 306] In this study, 2.2% of the non-institutionalized U.S. population are LTGS users while 4.5% reported use of oral glucocorticoid tablets. These percentages cannot be directly compared because: (1) the data of subjects in previous studies were obtained in 1996 while this study covers MEPS data from 1996 to 2004; and (2) different countries may have different prevalence rates. However, these percentages still provide useful information showing that a relatively low percent of the general population are glucocorticoid users.

Long-term glucocorticoid therapies were most frequently used for musculoskeletal and respiratory conditions. Previous research indicates that musculoskeletal and pulmonary diseases are two major categories of underlying conditions.[307, 308] This study shows similar results; for example, respiratory diseases (25.3%) and joint problems (21.9%) rank as the top two categories in LTGS users. Therefore, RCTs or observational studies for glucocorticoid-induced osteoporosis should not exclude subjects with the comobidities listed above.

The majority of glucocorticoid users were categorized into the racial group of white. In this study, 92.7% of MEPS subjects who used bisphosphonates were white while in a previous study 93.7% of those subjects were white.[309] In the white group of this study, the majority of MEPS female subjects used hormone replacement therapy,

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305 Gudbjornsson, B. *et al*. (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

306 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids in the United Kingdom. *QJM* 93(2): 105-111.

307 Boling, E. P. (2004). Secondary osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clinical Therapeutics* 26(1): 1-14.

308 van Staa, T. P. *et al*. (2002). The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporosis International* 13(10): 777-787.

309 Farley, J. F. *et al.* (2006) Racial variations in antiresorptive medication use: results from the 2000 Medical Expenditure Panel Survey (MEPS). *Osteoporosis International* 17(1): 395-404.

followed by bisphosphonates. The same pattern was observed in Farley's study.[310] This finding also echoes recommended use of HRT for postmenopausal women by many guidelines and consensus reports, as described in Chapter One.

5.1.2 Medication Use

A previous cohort study showed that 46.4% of female high-risk glucocorticoid users (≧90 days, ≧ 5 mg prednisone, aged 18 years old and over) received HRT and 18.3% received other anti-osteoporotic medications, while 8.9% of male glucocorticoid users received any osteoporotic medication.[311] In this study, 21.8% of female high-risk glucocorticoid (HRGS) users received HRT and 14.0% received other anti-osteoporotic medications; 2.2% of male glucocorticoid users received any osteoporotic medication. In both of these two studies, HRGS users were evaluated, about 90% of the study subjects are white and the period of data collection is two years. However, the Feldstein *et al.* study collected data from 2000 to 2001, a total of 575 subjects were excluded because of ineligibility of the HMO plan, and it used no weighted adjustments.

In the current study, significant differences in average ages and average glucocorticoid doses were found among treatment groups. For example, subjects in the bisphosphonate, HRT and control groups have a significantly higher average glucocorticoid dose than those in the calcitonin, raloxifene and HRT-bisphosphonate combination groups, but those in the HRT and control groups were younger than those in other groups (Table 4.1.6). The combined effects of younger age and more glucocorticoid use on fractures are unknown, but the effect of age on fractures was

310 *Ibid*

311 Feldstein, A. C. *et al*. (2005). Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. *Osteoporosis International* 16(12): 2168-2174.

partially controlled by categorizing study subjects into four age groups (as shown in Tables of Appendix B). However, the higher average glucocorticoid dose for subjects in bisphosphonate group likely implies a bias. Overall, it suggests that a potential selection bias should exist among treatment groups.

5.1.3 Prevalence and Incidence

According to the National Osteoporosis Foundation (NOF), an estimated 12.5% (10 million) of Americans aged 55 years old or more already have osteoporosis.[312] It was estimated in this study that the overall annual prevalence rate of osteoporosis and osteoporotic fractures are about 4.1% and 2.7%, respectively, in MEPS subjects aged 50 years old or older. The discrepancy in prevalence may be due to different sources of data, different methods of estimation, different reference periods (1996-2004 for this study) or different ranges of prevalence (e.g., annual vs. 10-year prevalence).

It was estimated by a previous two-year cross-sectional survey that 20% of long-term steroid (LTGS) users had osteoporosis or osteopenia, and 26% had fragility fractures.[313] In this study, the weighted annual prevalence rates in LTGS users are about 7.7% for osteoporosis and 3.8% for osteoporotic fractures. This study included more LTGS users (unweighted N=5,209) than those (N=191) in the previous study by Gudbjornsson *et al.* Additionally, the estimates in this study are weighted to represent nationally representative estimates. Moreover, this study does not include osteopenia and has more a restricted criterion for osteoporotic fractures, so the total numbers of

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312 National Osteoporosis Foundation (2004). America's bone health: the state of osteoporosis and low bone mass. 2002. National Osteoporosis Foundation. Washington, D. C. 22 pages.

313 Gudbjornsson, B. *et al*. (2002). Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of the Rheumatic Diseases* 61(1): 32-36.

osteoporosis and osteoporotic fractures are lower than those in the study by Gudbjornsson *et al.*

It was estimated from a hospital database that the incidence rates of osteoporotic fractures during 2001 in France were 2,312 and 7,567 per one million men and women aged over 45 years, respectively.[314] It is estimated in this study that the average annual incidence rates of osteoporotic fractures between 1996 and 2004 in the U.S. are 17,175 and 15,572 per 10^6 person-years (PY) for the non-institutionalized men and women, respectively. With respect to the impact of glucocorticoid use on fracture rates, it was estimated from a population-based cross-sectional study in the U.K. that the incidence rates of osteoporotic fractures is about 26,000 per 10^6 PY in glucocorticoid users with a daily dose of at least 7.5 mg.[315] In this study, the estimated annual incidence rates of osteoporotic fractures in the U.S. are 26,543 per 10^6 PY for all HRGS users. These two estimates are similar.

Previous studies have shown the relationship between incidence of fractures and glucocorticoid use. Compared to non-glucocorticoid users, it was reported in the literature that the relative risk (RR) of any osteoporotic fractures in oral glucocorticoid users is 1.75 (95% confidence interval [CI] 1.6-1.9),[316] 1.59 (95% CI 1.49-1.70)[317] or 1.33 (95% CI 1.29-1.38).[318] In this study, the RR of osteoporotic fractures is 1.15 (95% CI= 0.90-1.45) for LTGS users without prior exposure to osteoporosis and osteoporotic

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314 Maravic, M. *et al*. (2005). Incidence and cost of osteoporotic fractures in France during 2001. a methodological approach by the national hospital database. *Osteoporosis International* 16(12): 1475-1480.

315 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids and risk of fractures. *Journal of Bone and Mineral Research* 15(6): 993-1000.

316 Steinbuch, M. *et al*. (2004). Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporosis International*, 15(4): 323-328.

317 Vestergaard, P. *et al*. (2003). Corticosteroid use and risk of hip fracture: a population-based case-control study in Denmark. *Journal of Internal Medcine* 254: 486-493.

318 van Staa, T. P. *et al*. (2000). Use of oral corticosteroids and risk of fractures. *Journal of Bone and Mineral Research* 15(6): 993-1000.

fractures. As indicated by van Staa *et al.*,[319] different findings may be due to: (1) different sample sizes; (2) various definitions of glucocorticoid exposure, imprecise measurement of glucocorticoid doses or incomplete information on compliance; (3) different locations (femoral neck, spine, etc.) or methods (dual x-ray absorptiometry (DXA), quantitative computed tomography (QCT), etc.) of bone density measurement; and (4) inappropriate control group. In addition to these comments, there are different inclusion criteria for osteoporotic fractures. This study uses relatively restricted definitions of osteoporotic fractures, targets LTGS users which are different from those in previous studies, and, most importantly, involves effects from anti-osteoporotic treatments while other studies may not. A direct comparison among RRs is inappropriate, but the trend shows that use of glucocorticoid steroids increases the risks of osteoporotic fractures with or without use of anti-osteoporotic treatments.

Based on the logistic regression analyses, men in the WELL and GIFX states had higher odds of osteoporotic fractures than women in the same state, whereas women in the GIOP state have higher odds of osteoporotic fractures than men in the GIOP state. A possible explanation is that the prevalence rate of osteoporosis in women is relatively higher than in men so that women in the GIOP state may be proactive to any intervention which prevents osteoporotic fractures. For example, women are generally aware of consuming diary food for prevention of osteoporosis; these actions were not recorded in the MEPS data. The possibility that glucocorticoid users with osteoporosis may be proactive regarding anti-osteoporotic treatment can also explain why glucocorticoid users in the GIOP state have a relatively lower RR than those in other states.

319 *Ibid.*

The protective effects of bisphosphonates on bone mineral density (BMD) increases are significant in most RCTs, but the effects of bisphosphonates on osteoporotic fractures are inconsistent in the literature. For example, a one-year RCT showed that no significant differences in both prevalence and incidence rates of vertebral fractures were found between the alendronate and placebo groups (prevalence: 54% in the alendronate group and 39% in the placebo group, incidence: 13% in alendronate group and 4% in the placebo group).[320] Although the differences are not significant, both rates for alendronate group are higher than those for the placebo group. This is similar to the current study findings in that bisphosphonate groups have higher prevalence and incidence rates than the control groups.

5.1.4 Costs

The estimates of direct medical costs of osteoporotic fractures vary by population at risk, affected sites, year of estimates and countries in the literature. The estimated hospital costs of hip fractures ranged from U.S. $8,977 to $10,314 plus $752 to $7,897 per additional year[321, 322] or an overall estimate of $19,800.[323] The estimated hospital costs of vertebral and wrist fractures range from $790 to $1,255 and from $772 to $1,496, respectively[324, 325] In this study, the estimated average direct medical costs of all

320 Lems, W. F. *et al.* (2006). Positive effect of alendronate on bone minieal density and makers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. *Osteoporosis International* 17: 716-723.

321 Reginster, J.-Y. *et al*. (1999). Direct costs of hip fractures in patients over 60 years of age in Belgium. *Pharmacoeconomics* 15(5): 507-514.

322 $1 USD =0.84219 Euro, as of Jan. 4, 1999. URL: http://www.geocities.com/eureka/concourse/8751/tabl-er2.htm Accessed July 12, 2007.

323 1£=$1.6120-1.7255 in 1998, URL: http://www.taxfreegold.co.uk/1998forexrates.html Accessed July 12, 2007.

324 Dolan, P. & Torgerson, D. J. (1998). The cost of treating osteoporosis fractures in the United Kingdom female population. *Osteoporosis International* 8(6): 611-617.

osteoporotic fractures in the U.S. non-institutional population are $5,300 for the first-time episode and $9,100 for a repeated episode (Table 4.3.2). The disparity in cost estimations may arise because this study calculates overall average costs of osteoporotic fractures at different sites and includes costs from sources other than hospital stays.

The average wholesale prices (AWP) for one-year supplies of risedronate (5 mg/day), alendronate (5-and 10-mg/day) and conjugated estrogen (0.625 mg/day) are $668,[326] $762 and $75,[327] respectively. The AWP of a prescribed medication is usually the "list price" of the medication, and has been used in calculations for pricing or reimbursements.[328] However, AWP does not reflect the actual market price of a medication because actual prices involve various discounts for reimbursement. The use of "real-world" costs in cost analyses is becoming notable in the literature. For example, recent studies reported that the medication costs in the first year after a non-vertebral fracture are $320, $110 and $512 for alendronate, risedronate and calcitonin, respectively,[329] and that the average costs for GI-related adverse reactions are $72 for alendronate and $26 for risedronate.[330]

The estimated costs of anti-osteoporotic treatments in this study are different from those reported in previous studies. It is estimated in this study that the average costs

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325 Gabriel, S. E. *et al*. (2002). Direct medical costs attributable to osteoporosis fractures. *Osteoporosis International* 13(4): 323-330.

326 Wyman, M. (2000). *Pharmacotherapy Update* 3(3) Cleveland Clinic Foundation. http://clevelandclinicmeded.com/medical_info/pharmacy/aug2000/pharm.htm

327 Buckley, L. M. & Hillner, B. E. (2003). A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *Journal of Rheumatology* 2003 30(1): 132-138.

328 Gencarelli, D. M. (2002). Average wholesale price for prescription drugs: is there a more appropriate pricing mechanism? *National Health Policy Forum Issue Brief* 775:1-19.

329 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

330 Kane, S. *et al.* (2004). Pharmacoeocnomic evaluation of gastrointestinal tract events during treatment with risedronate or alendronate: a retrospective cohort study. *The American Journal of Managed Care*, 10(7): S216-S226.

(including costs for treatments of GI-related adverse reactions) per MEPS subject for prevention of osteoporotic fractures are $388 in the bisphosphonate group and $299 in the calcitonin group. Table 4.3.4 also shows that the average annual prescription costs per MEPS subject are $324 for bisphosphonates and $247 for calcitonin. If costs for treatments of existing osteoporotic fractures are included, the annual average total fracture-related costs per MEPS subject are $816 in the bisphosphonate group and $617 in the calcitonin group. The "real-world" costs are lower than AWP likely due to discounts and free samples received in study subjects. The reasons for disparity in estimated costs between this and previous studies include different inclusion criteria for costs, inflation in later years and different sampling frames (e.g., regions, hospitals, etc.).

5.1.5 Long-Term Cost-Effectiveness

No significant difference in long-term effectiveness of anti-osteoporotic treatments was found for the 30-year-old and 65-year-old female cohorts with two-year or 10-year simulations and for 50-year-old female cohorts with lifetime simulations. Significant differences in long-term effectiveness of anti-osteoporotic treatments were found for the 30-year-old and 65-year-old female cohorts with lifetime simulations and for the 50-year-old female cohorts with two-year or 10-year simulations. If costs of anti-osteoporotic treatments are not considered at this moment, the current study suggested that 50-year-old female glucocorticoid users should selecte a preferred treatment based on short-term effectiveness and 30-year-old and 65-year-old female glucocorticoid users select a preferred treatment based on lifetime effectiveness.

Explanations for these findings are discussed as follows. The younger (30-year-old) women have relatively healthy bones overall and the older (65-year-old)

women have a relatively low bone mass overall, so the differences between anti-osteoporotic treatments in osteoporotic fractures were too small to be detected in a short perioid of time (two years or 10 years). The differences in osteoporotic fractures for 50-year-old women may be due to menopausal status, and anti-osteoporotic treatments have a protective effect on vertebral fractures, which are frequently observed in post-menopausal women. Anti-osteoporotic treatments likely show differences in effectiveness for 50-year-old women in a short period of time.

Compared with no treatment, Homik *et al.* estimated that the 10-year incremental costs per vertebral fracture avoided were $9,000 in bisphosphonate treatment for hypothetical young female glucocorticoid users;[331] Buckley and Hillner estimated that the 10-year and lifetime incremental costs per vertebral fracture avoided were $7,883-$121,125 (10-year) or $4,122-$7,883 (lifetime) in alendronate treatments for hypothetical Caucasian female glucocorticoid users with different ages and BMD measurements.[332] In this study, the estimated 10-year and lifetime incremental cost per osteoporotic fracture avoided are $27,253 to $35,692 (10-year) and $84,942 to $91,075 (lifetime) in hypothetical female glucocorticoid users with different ages. In comparison to these two studies., this study has at least three differences: (1) this study used higher annual costs of bisphosphonate treatments ($1,035 in Table 4.3.1 vs. $780 in the Homik *et al.* study vs. $762 in Buckley and Hillner's study) because this study includes costs for all medical events in addition to pharmacy costs; (2) this study estimates cost-effectiveness for all osteoporotic fractures while the other two studies

331 Homik, J. E. *et al*. (1998). Cost-effectiveness of bisphosphonates in the prevention of corticosteroid-induced osteoporosis. *Arthritis and Rheumatism* 4(Suppl. 9): S303.

332 Buckley, L. M. & Hillner, B. E. (2003). A cost effectiveness analysis of calcium and vitamin D supplementation, etidronate, and alendronate in the prevention of vertebral fractures in women treated with glucocorticoids. *Journal of Rheumatology* 2003 30(1): 132-138.

addressed vertebral fractures only; and (3) three studies used different Markov models and specifications for osteoporosis and osteoporotic fractures.

This comparison indicates that different methodologies and models yield different estimates of long-term cost-effectiveness of bisphosphonate treatment in female glucocorticoid users. It is relatively difficult to directly compare study findings with each other. This situation echoes with the need for model transparency based on principles of good practice for modeling suggested by the International Society for Pharmacoeconomics and Outcomes and Research (ISPOR) Task Force Panel.[333, 334] Cost-effectiveness analyses involving modeling techniques should explicitly describe the methodology and model specifications, so that study findings are comparable with each other.

The current study projected that HRT was the most cost-effective option for female glucocorticoid users in most long-term estimations. The findings about hormone replacement therapy (HRT) in this study were based on MEPS data from 1996 to 2004 when HRT was still a recommended option for osteoporosis. However, HRT is currently not recommended for post-menopausal women for prevention of vertebral fractures in general based on the findings of Women Health Initiative (WHI) study.[335, 336] The study included insufficient information about the adverse drug events resulting from HRT, so it is questionable to apply the long-term estimates of HRT in this study to

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333 Garrison, L. P. (2003) The ISPOR good practice modeling principles-a sensible approach: be transparent, be reasonable. *Value in Health* 6(1): 6-8.

334 Weinstein, M. C. *et al.* (2003). Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on good research practice-modeling studies. *Value in Health* 6(1): 9-17.

335 Kleerekoper, M. (2002). Lessons from the skeleton: was the Women's Health Initiative (WHI) a primary prevention trial? *Osteoporosis International* 13(9): 685-687.

336 Majumdar, S. R. *et al*. (2004). Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *Journal of the American Medical Association* 292(16): 1983-1988.

current clinical practices. If HRT will be used in female glucocorticoid users, adverse drug reactions should be cautiously monitored.[337]

When HRT is not considered, based on study findings, raloxifene is the most cost-effective option for prevention of glucocorticoid-induced fractures in young (30-year-old or 50-year-old) women who receive glucocorticoid therapy for less than 10 years, while calcitonin is the most cost-effective option in older (65-year-old) women who receive glucocorticoid therapy for less than 10 years. Nasal calcitonin is the cost-effective option for prevention of glucocorticoid-induced fractures in women at any age who receive glucocorticoid therapy over 10 years.

5.1.6 Managed Care

From the perspective of managed care, the incremental cost-effectiveness ratios (ICERs) can be translated to an average additional expense to avoid one episode of osteoporotic fracture in 10,000 long-term glucocorticoid users. For example, compared to the strategy of regular monitoring for osteoporosis, the total osteoporosis-related expenditures for 50-year-old female glucocorticoid users receiving bisphosphonate therapy to avoid one episode of osteoporotic fracture were $29,586 for two years and $35,692 for 10 years, respectively (Table 4.5.2). As Barrington *et al.* pointed out, an explanation based on return on investment (ROI) is more relavent to payers in settings of managed care.[338] By using the same example, the average annual costs related to osteoporosis for female glucocorticoid users receiving bisphosphonate therapy were

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337 American College of Rheumatology (ACR) (2001). Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on glucocoritcoid-induced osteoporosis. *Arthritis and Rheumatism* 44(7): 1496-1503.

338 Barrington, C. *et al.* (2006). Managing osteoporosis in a managed care population. *The f* 12(7) S199-202.

$14,793 (two years) and $3,569 (10 years), respectively; the saving is $11,224 in the 10th years. In other words, compared to the current annual total osteoporosis-related expenditures for female glucocorticoid users to avoid an osteoporosis fracture, payers will pay less ($11,224) after 10 years. Therefore, for every dollar invested within two years, payers will receive an ROI of $0.76 ($11,224/$14,793) after 10 years.

5.2 STUDY LIMITATIONS

Due to the study design and the nature of the data sources, some study limitations are presented. Limitations restrict the applications of study results or methodology for other uses. Acknowledging these limitations helps with the interpretation of study results and drawing reasonable conclusions.

(1) **Assignment of dates for events in MEPS.** A notable source of uncertainty in this study is the assignment of dates for events of osteoporosis, fractures and prescriptions if the data are missing. These dates are critical in this study because they were used to determine the incidence of osteoporosis and osteoporotic fractures (i.e., new episodes after the use of anti-osteoporotic treatment) and prior exposure to osteoporosis and osteoporotic fractures which determine the percentage of subjects in the initial Markov states. The use of a proxy (i.e., the reference date of the corresponding round that events occurred) solved the problem of missing data, but uncertainty remains. The sensitivity analyses did not address this issue.

(2) **Selection bias.** Potential selection biases were found in this study, especially for subjects receiving bisphosphonate therapy. The current study indicates that

glucocorticoid users receiving bisphosphonate therapy had relatively higher average daily glucocorticoid doses than those in other groups. It is uncertain whether or not glucocorticoid users receiving bisphosphonate therapy have more severe comorbid conditions and/or worse bone health at the baseline. The potential selection bias has important implications for both the internal validity and the generalizability of the study findings.

(3) **Costs**. The estimation of weighted costs does not reflect the actual costs. The costs for treating the underlying conditions are not considered for this study. Utilization of medical services for the underlying diseases may vary among glucocorticoid users with different disease states and conditions. The costs for laboratory tests were not considered separately but have been included in costs for events.

(4) **Osteoporotic fractures**. Because osteoporosis and non-symptomatic vertebral fractures are believed to be under-diagnosed, their true incidence is likely to be under-estimated. All estimates are based on retrospective data (1996-2004), so the study results may not represent current status. In addition, both the underlying diseases and the use of glucocorticoid steroids contribute to the risks of fractures; it is difficult to isolate the portion solely due to glucocorticoid therapy, or the protective effects due to the use of anti-osteoporotic agents.

Another challenge in this study was to estimate incidence rates as model inputs because of small sample sizes for estimation in some cases. These estimates were indirectly derivated from relative risks which were calculated based on study data, so there is still some uncertainty for estimations. Sensitivity analyses address part of this issue by varying 30% above and below averages in transition probabilities.

Nonetheless, this study provides "real-world" up-to-date information about prevalence and incidence of osteoporosis and osteoporotic fractures.

(5) **Confounding factors.** The control of all confounding factors is limited. Age is a confounding factor for osteoporotic fractures, but it has been partially controlled by dividing study subjects into four age groups. The incidence rates of osteoporotic fractures were calculated for each age group. The underlying conditions, use of glucocorticoid steroids,and prior use of anti-osteoporotic treatments, were not controlled in this study. Other potential confounding factors, such as psycho-social factors and other medications (e.g., anti-convulsants) that have an impact on fractures, were not considered in this study.

(6) **Secondary database.** Because MEPS datasets are secondary databases, they are subject to limitations recognized for secondary databases. Some articles have discussed possible limitations for retrospective databases.[339, 340, 341] There is little control over the existing data in terms of selection of survey samples, information collected, data quality, input errors and possible selection bias. For example, values of lab tests desired for this study are not available in the MEPS data. Additionally, there is no way to trace information needed for unclear or missing values in MEPS. For example, participant-reported disease conditions may be incorrectly coded based on the 3-digit ICD-9-CM in the MEPS datasets, and that cannot be validated. There is no

339 Arnold, R. G. *et al.* (1999). Panel 3: Methodological issues in conducting pharmacoeconomic evaluations-retrospective and claims database studies. *Value in Health* 2(2): 82-87.

340 Motheral, B. *et al.* (2003). A checklist for retrospective database studies-report of the ISPOR task force on retrospective databases. *Value in Health* 6(2): 90-97.

341 Brixner, D. (2006). Assessment of the prevalence and costs of osteoporosis treatment options in a real-world setting. *The American Journal of Managed Care*, 12(7 Supple.): S191-S198.

control over some variables of interest, such as records for calcium and vitamin D which may be incomplete in MEPS. However, MEPS attempts to clean and validate much of its data. The overall MEPS data is relatively reliable and accurate.

(7) **Generalizability.** Because some non-responses occurred in the MEPS surveys, limitations in generalizability apply to the MEPS data. Even though MEPS is designed to generate national estimates for the U.S. civilian non-institutionalized population, the MEPS samples may be not representative of the target population. Furthermore, the ability to generalize the study results to populations other than the U.S. civilian non-institutionalized population is limited.

5.3 DIRECTIONS OF FUTURE RESEARCH

The sample size of some subgroups in this study was too small to have enough statistical power to detect differences in osteoporotic fractures among treatment groups. A database with a larger sample size may achieve sufficient statistical power. Additionally, databases with clear records for dates of events (episodes of osteoporosis, fractures and prescriptions) and detailed diagnosis codes are preferable. Also, databases should cover a timeframe that is long enough (for example, at least three years for each individual) to detect differences in osteoporotic fractures. Furthermore, adverse drug reactions should be carefully studied again by using up-to-date data since HRT and bisphosphonates have received more attention recently. Considerations of selection bias and the inclusion of more confounding factors will clarify uncertainty and facilitate comparisons of cost-effectiveness among treatment groups.

5.4 RECOMMENDATIONS AND CONCLUSIONS

This study provides up-to-date epidemiological information on prevalence and incidence rates of osteoporosis and osteoporotic fractures in the U.S. A relatively low percentage of long-term glucocorticoid users received anti-osteoporotic treatments for prevention of glucocorticoid-induced osteoporosis and osteoporotic fractures. This study is the first research using "real-world" nationally representative information to estimate long-term costs and effectiveness of anti-osteoporotic treatments for glucocorticoid-induced osteoporosis and osteoporotic fractures. Most inputs for the Markov model were derived from "real-world" data so the study results should reflect realilties of treatments. Cost-effectiveness analyses compared long-term estimates of costs and effectiveness for hypothetical cohorts with different ages and length of treatments, and the following anti-osteoporotic treatements are recommended.

It is recommended that hormone replacement therapy may still be used in pre-menopausal women receiving long-term glucocorticoid therapy with careful monitoring adverse drug reactions, but the evidence of safety needs further investigation. Raloxifene could be recommended as an alternative to HRT, but evidence in glucocorticoid users is needed. Calcitonin is cost-effective in post-menopausal women and men of all ages who receive long-term glucocorticoid therapy. Bisphosphonates are less cost-effective in most cases which may be due to selection bias. Overall, use of anti-osteoporotic treatments is recommended for long-term glucocorticoid users in comparison to the controls. The final decision of treatment selection depends on age, length of glucocorticoid therapy and maximal allowance of payments.

APPENDIX A-IRB Letter of Approval

OFFICE OF RESEARCH SUPPORT & COMPLIANCE

THE UNIVERSITY OF TEXAS AT AUSTIN

P.O. Box 7426, Austin, Texas 78713 (512) 471-8871 - FAX (512 471-8873)
North Office Building A, Suite 5.200 (Mail code A3200)

FWA# 2030

Date: **02/08/07**

PI(s): **Jun-Yen Yeh** Department & Mail Code: **PHAR-PHARMACY ADMIN** **A1930**

Kenneth A Lawson **PHAR-PHARMACY ADMIN** **A1930**

Dear: **Jun-Yen Yeh** **Kenneth A Lawson**

IRB APPROVAL – IRB Protocol # **2007-01-0094**

Title: **Cost-Effectiveness Analyses of Anti-Resorptive Agents for Management of Glucocorticoid-Induced Osteoporosis and Fractures: Empirical Estimates from the 1996-2004 MEPS Data and Longitudinal Projection from Markov Modeling**

In accordance with Federal Regulations for review of research protocols, the Institutional Review Board has reviewed the exempt status assessment of the above referenced protocol and found that it meets exempt approval under the category designated below for the following period: **02/08/2007** - **02/07/2008**

Any research involving surveys, interviews, or observation of children is not eligible for exempt review, unless it consists only of observational research where the investigator(s) do not participate in the activities being observed. Research that is FDA regulated cannot be granted an exemption except for category 6. (Research is FDA-regulated when it involves the use of a drug or medical device, other than the use of an approved drug or medical device in the course of medical practice, or when the results are to be submitted to or held for inspection by the FDA.) Unless otherwise required by Department or Agency heads, exempt research must fall within one of the following categories:

___1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

(i) research on regular and special education instructional strategies, or
(ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
(iii). The research is not FDA-regulated

___2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i.) Information obtained is recorded in such a manner that human subjects can be identified, directly or through

identifiers linked to the subjects: and
(ii.) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation; or
(iii.) The research involves surveys, interviews, or observation of children (where the investigator does not participate in the activities being observed);
(iv.) The research is not FDA-regulated

___3. Research involving the use of educational tests, survey or interview procedures, or observing public behavior that is not exempt under number 2 above, if the subjects are public officials or candidates for public office or a federal statute requires that the confidentiality of personally identifiable information will be maintained throughout the research and thereafter. The research is not FDA-regulated

_x_ 4. Research involving the collection or study of existing data, documents, records, pathological or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects. To qualify for exemption, the data, documents, records or specimens must be in existence before the project begins. The research is not FDA-regulated

___5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate; or otherwise examine:

i. Public benefit or service programs;
ii. Procedures for obtaining benefits or services under those programs;
iii. Possible changes in-or alternatives to those programs or procedures; or
iv. Possible changes in methods or levels of payment for benefits or services under those programs.
v. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
vi. The research or demonstration project must be conducted pursuant to specific federal statutory authority;
vii. There must be no statutory requirement that an IRB review the project;
viii. The project must not involve significant physical invasions or intrusions upon the privacy of participants;
ix. The funding agency must authorize or concur with this exemption.
x. The research is not FDA-regulated

___6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

____Please use the attached approved consent forms

____Waiver of Documentation of Consent

_x_Waiver of Informed Consent

RESPONSIBILITIES OF PRINCIPAL INVESTIGATOR FOR ONGOING PROTOCOLS:

(1) Report immediately to the IRB any unanticipated problems.
(2) Proposed changes in approved research during the period for which IRB approval cannot be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to participant. Changes in approved research initiated without IRB review and approval to eliminate apparent immediate hazards to the participant must be promptly reported to the IRB, and reviewed under the unanticipated problems policy to determine whether the change was consistent with ensuring the participants continued welfare.
(3) Report any significant findings that become known in the course of the research that might affect the willingness of subjects to continue to take part.
(4) Insure that only persons formally approved by the DRC enroll subjects.
(5) If relevant to your study, please use only a currently approved consent form (remember approval periods are for 12 months or less).
(6) Protect the privacy and confidentiality of all persons and personally identifiable data, and train your staff and collaborators on policies and procedures for ensuring the privacy and confidentiality of participants and information.
(7) Submit for review and approval by the IRB all modifications to the protocol or consent form(s) prior to the implementation of the change.
(8) Please note that this office will send out a reminder prior to the end of your approval period (typically at the end of the 12 months). At this time we will ask you to give us an update on whether the study is still in progress and/or has had any changes that need to be reviewed for approval.
(9) Notify the IRB and the DRC when the study has been completed and complete the Final Report Form.
(10) Please help us help you by including the above protocol number on all future correspondence relating to this protocol.

Thank you for your help in this matter.

Sincerely,

Lisa Leiden

Lisa Leiden Ph.D., IRB Chair.
Director of the Office of Research, Support, & Compliance

APPENDIX B-Incidence Rates of Osteoporosis and Osteoporotic Fractures by Gender, Type of Subject, Age Groups and Treatments

Table B.1 Incidence of osteoporosis in MEPS female subjects without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

MEPS female	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	6	101,101	0	-	-	-	-
CN	0	0	0	-	-	-	-
HB	2	21,148	0	-	-	-	-
HT	1,825	23,026,192	0	-	-	-	-
RF	0	0	0	-	-	-	-
CT	23,059	221,261,906	9	73,910	24.4	334	84
31-50							
BP	50	520,540	16	112,096	46.6	215,346	58,827
CN	10	118,669	2	28,222	40.6	237,821	65,640
HB	20	204,077	2	23,514	48.6	115,221	30,141
HT	3,655	39,885,186	18	171,219	45.3	4,293	1,075
RF	20	166,356	1	9,565	48.0	57,497	14,695
CT	26,744	262,308,892	69	486,035	44.3	1,853	464
51-70							
BP	293	2,997,543	92	911,586	62.9	304,111	86,655
CN	37	461,249	10	97,693	64.7	211,801	57,766
HB	140	1,438,736	40	393,339	63.0	273,392	76,738
HT	6,732	71,818,172	168	1,818,805	61.4	25,325	6,392
RF	198	2,261,730	40	442,311	62.6	195,563	52,950
CT	12,131	113,479,390	197	1,920,893	62.2	16,927	4,259
71-90							
BP	363	3,812,364	134	1,465,216	78.7	384,333	114,198
CN	73	725,946	18	223,989	77.3	308,548	88,114
HB	82	902,154	31	346,713	75.7	384,317	114,193
HT	1,304	14,024,126	65	763,320	75.8	54,429	13,894
RF	121	1,291,312	23	256,099	75.5	198,325	53,764
CT	8,053	80,115,975	265	2,696,664	79.6	33,660	8,523

Ave.=average; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.2 Incidence of the first osteoporotic fracture in MEPS female subjects without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

MEPS female	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	6	101,101	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	2	21,148	0	-	-	-	-
HT	1,825	23,026,192	20	210,463	24.5	9,140	2,293
RF	0	-	0	-	-	-	-
CT	23,050	221,187,996	197	2,170,695	20.8	9,814	2,463
31-50							
BP	50	520,540	0	-	-	-	-
CN	10	118,669	0	-	-	-	-
HB	20	204,077	2	23,514	48.6	115,221	30,141
HT	3,655	39,885,186	55	581,344	45.4	14,575	3,664
RF	20	166,356	0	-	-	-	-
CT	26,675	261,822,856	266	2,784,405	41.2	10,635	2,669
51-70							
BP	293	2,997,543	8	93,369	66.3	31,149	7,880
CN	37	461,249	5	59,490	69.6	128,976	33,932
HB	140	1,438,736	4	29,069	59.0	20,205	5,090
HT	6,732	71,818,172	106	1,073,713	57.7	14,950	3,759
RF	198	2,261,730	4	39,464	57.6	17,449	4,391
CT	11,934	111,558,497	180	1,776,554	60.0	15,925	4,005
71-90							
BP	363	3,812,364	14	179,481	80.4	47,079	11,983
CN	73	725,946	10	89,874	78.1	123,803	32,501
HB	82	902,154	2	13,062	83.4	14,479	3,639
HT	1,304	14,024,126	58	691,242	78.5	49,289	12,557
RF	121	1,291,312	2	26,202	72.6	20,291	5,112
CT	7,788	77,419,310	308	3,386,429	81.8	43,741	11,119

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.3 Incidence of the first osteoporotic fracture in MEPS female subjects with prior osteoporosis by age and treatment group, MEPS 1996-2004

MEPS female	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	9	73,910	0	-	-	-	-
31-50							
BP	11	120,807	0	-	-	-	-
CN	8	88,141	0	-	-	-	-
HB	12	141,035	2	31,164	49.5	220,966	60,517
HT	12	72,071	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	69	486,035	4	28,468	40.4	58,572	14,976
51-70							
BP	212	2,215,563	2	15,002	64.5	6,771	1,697
CN	34	386,268	0	-	-	-	-
HB	95	1,010,987	2	14,173	53.5	14,019	3,523
HT	80	742,190	0	-	-	-	-
RF	33	320,264	0	-	-	-	-
CT	197	1,920,893	10	98,642	61.0	51,352	13,093
71-90							
BP	271	3,024,983	17	225,749	80.1	74,628	19,203
CN	44	620,016	0	-	-	-	-
HB	39	528,471	2	33,567	78.4	63,517	16,272
HT	34	329,750	2	16,124	71.3	48,898	12,455
RF	34	350,523	2	22,569	76.4	64,387	16,501
CT	265	2,696,664	29	314,654	79.3	116,683	30,542

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.4 Incidence of repeated osteoporotic fracture in MEPS female subjects with prior fracture by age and treatment group, MEPS 1996-2004

MEPS female	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	7	119,897	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	203	2,225,590	6	54,895	19.8	24,665	6,224
31-50							
BP	4	55,393	0	-	-	-	-
CN	2	16,859	0	-	-	-	-
HB	2	31,164	2	31,164	49.5	-	-
HT	24	202,537	10	77,938	44.7	384,809	114,370
RF	0	-	0	-	-	-	-
CT	288	3,011,254	18	198,381	38.6	65,880	16,893
51-70							
BP	16	137,511	9	97,985	65.9	712,561	267,789
CN	2	38,096	0	-	-	-	-
HB	6	47,759	2	6,719	56.5	140,686	37,196
HT	21	244,078	4	54,799	52.1	224,514	61,588
RF	2	12,321	0	-	-	-	-
CT	201	1,961,124	11	85,928	61.1	43,816	11,139
71-90							
BP	50	566,786	11	140,804	80.4	248,425	68,907
CN	25	279,526	4	29,314	75.5	104,870	27,317
HB	5	50,239	2	22,863	78.6	455,085	140,824
HT	10	57,420	5	27,530	78.2	479,450	150,593
RF	5	53,377	2	27,651	79.5	518,032	166,790
CT	372	4,130,982	41	429,899	84.3	104,067	27,098

Ave.=average; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.
§N=total number of subjects from 1996 to 2004.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
**Rates per 1,000,000 person-years.

Table B.5 Incidence of osteoporosis in long-term glucocorticoid female users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

LTGS female	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	2	53,175	0	-	-	-	-
CN	0	0	0	-	-	-	-
HB	2	21,148	0	-	-	-	-
HT	36	539,762	0	-	-	-	-
RF	0	0	0	-	-	-	-
CT	323	3,138,236	4	22,213	15.9	7,078	1,774
31-50							
BP	12	70,028	4	24,976	41.1	356,657	104,407
CN	3	38,095	2	28,222	40.6	740,832	286,498
HB	2	18,999	0	-	-	-	-
HT	139	1,506,334	0	-	-	-	-
RF	0	0	0	-	-	-	-
CT	871	9,371,402	10	62,227	39.1	6,640	1,664
51-70							
BP	22	187,146	10	93,832	64.0	501,384	159,686
CN	9	68,463	4	38,217	64.1	558,214	184,727
HB	15	138,181	4	24,442	64.4	176,884	47,499
HT	385	4,152,260	9	127,423	63.5	30,688	7,762
RF	2	15,563	0	-	-	-	-
CT	570	5,394,771	11	114,504	64.2	21,225	5,349
71-90							
BP	28	225,394	5	22,852	75.3	101,387	26,372
CN	4	56,241	2	22,740	71.5	404,331	121,481
HB	13	108,572	10	89,483	78.5	824,181	352,460
HT	102	990,721	7	68,762	73.5	69,406	17,822
RF	5	31,502	0	-	-	-	-
CT	349	3,544,572	27	311,566	78.4	87,899	22,739

Ave.=average; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.6 Incidence of the first osteoporotic fracture in long-term glucocorticoid female users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

LTGS female	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	2	53,175	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	2	21,148	0	-	-	-	-
HT	36	539,762	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	319	3,116,023	4	56,953	16.1	18,277	4,601
31-50							
BP	12	70,028	0	-	-	-	-
CN	3	38,095	0	-	-	-	-
HB	2	18,999	0	-	-	-	-
HT	139	1,506,334	3	27,030	44.0	17,944	4,517
RF	0	-	0	-	-	-	-
CT	861	9,309,175	14	128,733	42.3	13,829	3,475
51-70							
BP	22	187,146	0	-	-	-	-
CN	9	68,463	0	-	-	-	-
HB	15	138,181	0	-	-	-	-
HT	385	4,152,260	4	32,599	53.4	7,851	1,969
RF	2	15,563	0	-	-	-	-
CT	559	5,280,267	8	58,823	63.6	11,140	2,797
71-90							
BP	28	225,394	0	-	-	-	-
CN	4	56,241	0	-	-	-	-
HB	13	108,572	0	-	-	-	-
HT	102	990,721	11	100,801	76.7	101,745	26,469
RF	5	31,502	0	-	-	-	-
CT	322	3,233,006	12	159,618	81.1	49,371	12,578

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.7 Incidence of the first osteoporotic fracture in long-term glucocorticoid female users with prior osteoporosis by age and treatment group, MEPS 1996-2004

LTGS female	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	4	22,213	0	-	-	-	-
31-50							
BP	3	26,358	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	3	40,898	0	-	-	-	-
HT	1	7,758	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	10	62,227	2	20,724	41.5	333,039	96,298
51-70							
BP	14	146,977	0	-	-	-	-
CN	4	72,069	0	-	-	-	-
HB	3	49,961	0	-	-	-	-
HT	18	144,031	0	-	-	-	-
RF	2	11,493	0	-	-	-	-
CT	11	114,504	2	19,374	59.4	169,199	45,284
71-90							
BP	25	299,319	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	2	11,085	0	-	-	-	-
HT	7	64,895	0	-	-	-	-
RF	2	26,787	0	-	-	-	-
CT	27	311,566	1	18,906	78.0	60,681	15,528

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.8 Incidence of repeated osteoporotic fracture in long-term glucocorticoid female users with prior fracture by age and treatment group, MEPS 1996-2004

LTGS female	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	4	56,953	0	-	-	-	-
31-50							
BP	2	16,515	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	3	18,519	1	8,182	50.0	441,817	135,641
RF	0	-	0	-	-	-	-
CT	16	149,456	0	-	-	-	-
51-70							
BP	3	20,154	1	13,258	70.0	657,835	235,180
CN	2	38,096	0	-	-	-	-
HB	2	6,719	2	6,719	56.5	1,000,000	-
HT	1	7,624	1	7,624	51.0	1,000,000	-
RF	0	-	0	-	-	-	-
CT	14	119,848	4	41,651	63.5	347,532	101,248
71-90							
BP	8	96,891	3	43,398	81.3	447,905	138,008
CN	2	8,310	0	-	-	-	-
HB	0	-	-	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	14	192,556	1	14,032	90.0	72,872	18,738

Ave.=average; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.9 Incidence of osteoporosis in high-risk glucocorticoid female users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

HRGS female	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	2	53,175	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	0	0	-	-	-	-
HT	21	283,084	0	-	-	-	-
RF	0	0	0	-	-	-	-
CT	230	2,246,282	4	22,213	15.9	9,889	2,481
31-50							
BP	12	70,028	4	24,976	41.1	356,657	104,407
CN	3	38,095	2	28,222	40.6	740,832	286,498
HB	2	18,999	0	-	-	-	-
HT	94	1,092,124	0	-	-	-	-
RF	0	0	0	-	-	-	-
CT	618	6,490,378	8	60,469	39.1	9,317	2,337
51-70							
BP	22	187,146	10	93,832	64.0	501,384	159,686
CN	9	68,463	4	38,217	64.1	558,214	184,727
HB	13	121,274	4	24,442	64.4	201,544	54,715
HT	286	3,152,208	5	53,769	66.2	17,058	4,292
RF	2	15,563	0	-	-	-	-
CT	428	3,927,152	11	114,504	64.2	29,157	7,370
71-90							
BP	23	165,013	4	13,835	76.8	83,842	21,654
CN	4	56,241	2	22,740	71.5	404,331	121,481
HB	11	99,239	10	89,483	78.5	901,692	440,052
HT	92	894,474	5	59,008	73.7	65,969	16,917
RF	5	31,502	0	-	-	-	-
CT	292	2,912,949	23	260,065	78.2	89,279	23,108

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.

**Rates per 1,000,000 person-years.

Table B.10 Incidence of the first osteoporotic fracture in high-risk glucocorticoid female users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

HRGS female	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	2	53,175	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	21	283,084	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	226	2,224,069	2	34,354	12.5	15,446	3,884
31-50							
BP	12	70,028	0	-	-	-	-
CN	3	38,095	0	-	-	-	-
HB	2	18,999	0	-	-	-	-
HT	94	1,092,124	2	18,848	41.4	17,258	4,343
RF	0	-	0	-	-	-	-
CT	610	6,429,910	8	49,741	46.0	7,736	1,940
51-70							
BP	22	187,146	0	-	-	-	-
CN	9	68,463	0	-	-	-	-
HB	13	121,274	0	-	-	-	-
HT	286	3,152,208	2	19,494	52.5	6,184	1,550
RF	2	15,563	0	-	-	-	-
CT	417	3,812,648	8	58,823	63.6	15,428	3,880
71-90							
BP	23	165,013	0	-	-	-	-
CN	4	56,241	0	-	-	-	-
HB	11	99,239	0	-	-	-	-
HT	92	894,474	11	100,801	76.7	112,693	29,449
RF	5	31,502	0	-	-	-	-
CT	269	2,652,884	9	119,853	79.4	45,178	11,491

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.
§N=total number of subjects from 1996 to 2004.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
**Rates per 1,000,000 person-years.

Table B.11 Incidence of the first osteoporotic fracture in high-risk glucocorticoid female users with prior osteoporosis by age and treatment group, MEPS 1996-2004

HRGS female	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	4	22,213	0	-	-	-	-
31-50							
BP	3	26,358	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	1	5,275	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	8	60,469	2	20,724	41.5	342,721	99,596
51-70							
BP	14	146,977	0	-	-	-	-
CN	4	72,069	0	-	-	-	-
HB	1	14,782	0	-	-	-	-
HT	17	137,833	0	-	-	-	-
RF	2	11,493	0	-	-	-	-
CT	11	114,504	2	19,374	59.4	169,199	45,284
71-90							
BP	19	216,598	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	2	11,085	0	-	-	-	-
HT	5	55,520	0	-	-	-	-
RF	2	26,787	0	-	-	-	-
CT	23	260,065	1	18,906	78.0	72,697	18,692

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HT=hormone replacement therapy; RF=raloxifene group; HB=simultaneously use of hormone replacement therapy and bisphosphonates.

**Rates per 1,000,000 person-years.

Table B.12 Incidence of repeated osteoporotic fracture in high-risk glucocorticoid female users with prior fracture by age and treatment group, MEPS 1996-2004

HRGS female	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	2	34,354	0	-	-	-	-
31-50							
BP	2	16,515	0	-	-	-	-
CN	0	-	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	2	10,338	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	10	70,464	0	-	-	-	-
51-70							
BP	3	20,154	1	13,258	70.0	657,835	235,180
CN	2	38,096	0	-	-	-	-
HB	2	6,719	2	6,719	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	12	94,545	2	16,348	68.4	172,912	46,352
71-90							
BP	6	64,923	1	11,430	71.0	176,055	47,260
CN	2	8,310	0	-	-	-	-
HB	0	-	0	-	-	-	-
HT	0	-	0	-	-	-	-
RF	0	-	0	-	-	-	-
CT	11	152,791	1	14,032	90.0	91,838	23,795

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.
§N=total number of subjects from 1996 to 2004.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent; HB=simultaneously use of hormone replacement therapy and bisphosphonates; HT=hormone replacement therapy; RF=raloxifene group.
**Rates per 1,000,000 person-years.

Table B.13 Incidence of osteoporosis in MEPS male subjects without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

MEPS male	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	0	0	-	-	-	-
CN	0	0	0	-	-	-	-
CT	18,836	194,768,392	3	18,260	16.0	94	23
31-50							
BP	5	57,222	0	-	-	-	-
CN	0	0	0	-	-	-	-
CT	21,928	242,313,124	11	120,701	42.2	498	125
51-70							
BP	23	252,159	12	150,917	61.9	598,499	203,984
CN	10	76,889	0	-	-	-	-
CT	16,456	174,961,092	42	409,088	61.6	2,338	585
71-90							
BP	15	130,674	4	35,627	78.1	272,640	76,499
CN	16	144,585	2	17,761	90.0	122,841	32,236
CT	7,011	75,156,326	34	270,738	78.2	3,602	902

Ave.=average; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.14 Incidence of the first osteoporotic fracture in MEPS male subjects without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

MEPS male	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	18,833	194,750,132	306	3,455,070	19.6	17,741	4,465
31-50							
BP	5	57,222	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	21,917	242,192,423	395	4,376,472	40.5	18,070	4,548
51-70							
BP	23	252,159	2	10,005	69.6	39,677	10,070
CN	10	76,889	1	4,653	70.0	60,516	15,485
CT	16,414	174,552,004	252	2,679,960	58.4	15,353	3,861
71-90							
BP	15	130,674	0	-	-	-	-
CN	16	144,585	1	5,087	71.0	35,183	8,914
CT	6,977	74,885,587	160	1,905,389	78.0	25,444	6,423

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.15 Incidence of the first osteoporotic fracture in MEPS male subjects with prior osteoporosis by age and treatment group, MEPS 1996-2004

MEPS male	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	1	33,749	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	3	18,260	0	-	-	-	-
31-50							
BP	4	15,555	0	-	-	-	-
CN	2	11,380	0	-	-	-	-
CT	11	120,701	0	-	-	-	-
51-70							
BP	2	17,164	0	-	-	-	-
CN	2	14,913	0	-	-	-	-
CT	42	409,088	0	-	-	-	-
71-90							
BP	14	166,210	0	-	-	-	-
CN	4	57,426	2	10,580	78.5	184,237	49,634
CT	34	270,738	2	9,308	80.6	34,380	8,708

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.16 Incidence of repeated osteoporotic fracture in MEPS male subjects with prior fracture by age and treatment group, MEPS 1996-2004

MEPS male	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	319	3,571,355	13	116,285	20.8	32,560	8,241
31-50							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	426	4,704,402	31	327,930	40.9	69,707	17,902
51-70							
BP	4	23,320	2	10,005	69.6	429,031	130,733
CN	0	-	0	-	-	-	-
CT	277	2,878,399	25	198,439	60.0	68,941	17,700
71-90							
BP	0	-	0	-	-	-	-
CN	4	82,435	0	-	-	-	-
CT	179	2,134,940	17	220,244	81.1	103,162	26,853

Ave.=average; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.17 Incidence of osteoporosis in long-term glucocorticoid male users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

LTGS male	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	0	0	-	-	-	-
CN	0	0	0	-	-	-	-
CT	336	3,340,638	0	-	-	-	-
31-50							
BP	2	27,848	0	-	-	-	-
CN	0	0	0	-	-	-	-
CT	464	5,225,046	2	20,558	46.4	3,935	985
51-70							
BP	8	49,820	4	32,773	61.9	657,828	235,177
CN	3	20,689	0	-	-	-	-
CT	609	6,357,296	3	23,438	57.2	3,687	923
71-90							
BP	8	46,418	2	6,626	72.5	142,746	37,773
CN	3	16,854	0	-	-	-	-
CT	350	3,984,542	2	23,981	71.5	6,019	1,508

Ave.=average; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.18 Incidence of the first osteoporotic fracture in long-term glucocorticoid male users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

LTGS male	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	336	3,340,638	5	41,649	23.8	12,467	3,132
31-50							
BP	2	27,848	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	462	5,204,488	11	147,590	38.9	28,358	7,166
51-70							
BP	8	49,820	0	-	-	-	-
CN	3	20,689	1	4,653	70.0	224,902	61,706
CT	606	6,333,858	18	248,099	59.3	39,170	9,940
71-90							
BP	8	46,418	0	-	-	-	-
CN	3	16,854	1	5,087	71.0	301,827	85,906
CT	348	3,960,561	10	117,745	79.6	29,729	7,517

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.19 Incidence of the first osteoporotic fracture in long-term glucocorticoid male users with prior osteoporosis by age and treatment group, MEPS 1996-2004

LTGS male	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	0	-	0	-	-	-	-
31-50							
BP	2	6,236	0	-	-	-	-
CN	2	11,380	-	-	-	-	-
CT	2	20,558	0	-	-	-	-
51-70							
BP	2	17,164	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	3	23,438	0	-	-	-	-
71-90							
BP	4	68,323	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	2	23,981	0	-	-	-	-

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.20 Incidence of repeated osteoporotic fracture in long-term glucocorticoid male users with prior fracture by age and treatment group, MEPS 1996-2004

LTGS male	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	5	41,649	0	-	-	-	-
31-50							
BP	0	-	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	12	163,371	1	15,781	43.0	96,596	25,077
51-70							
BP	0	-	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	20	260,813	2	12,714	65.3	48,748	12,416
71-90							
BP	0	-	0	-	-	-	-
CN	0	-	-	-	-	-	-
CT	10	117,745	0	-	-	-	-

Ave.=average; LTGS=long-term users of glucocorticoid tablets for at least three months; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.21 Incidence of osteoporosis in high-risk glucocorticoid male users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

HRGS male	WELL state		Osteoporosis			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N[§]	Wtd. N[§]	Unwtd N[§]	Wtd. N[§]	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	0	0	-	-	-	-
CN	0	0	0	-	-	-	-
CT	251	2,567,643	0	-	-	-	-
31-50							
BP	2	27,848	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	362	4,014,215	0	-	-	-	-
51-70							
BP	8	49,820	4	32,773	62.9	657,828	235,177
CN	3	20,689	-	-	-	-	-
CT	479	4,997,670	3	23,438	57.2	4,690	1,175
71-90							
BP	6	35,811	2	6,626	72.5	185,027	49,864
CN	3	16,854	0	-	-	-	-
CT	286	3,279,505	2	23,981	71.5	7,312	1,833

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Osteoporosis=new events of osteoporosis occurred after the treatment; Wtd=weighted; Unwtd=unweighted.

[§]N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.22 Incidence of the first osteoporotic fracture in high-risk glucocorticoid male users without prior osteoporosis and fracture by age and treatment group, MEPS 1996-2004

HRGS male	WELL state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	251	2,567,643	4	31,412	26.6	12,234	3,073
31-50							
BP	2	27,848	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	362	4,014,215	8	131,442	38.2	32,744	8,289
51-70							
BP	8	49,820	0	-	-	-	-
CN	3	20,689	1	4,653	70.0	224,902	61,706
CT	476	4,974,232	15	218,038	59.5	43,834	11,143
71-90							
BP	6	35,811	0	-	-	-	-
CN	3	16,854	1	5,087	71.0	301,827	85,906
CT	284	3,255,524	10	117,745	79.6	36,168	9,167

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.23 Incidence of the first osteoporotic fracture in high-risk glucocorticoid male users with prior osteoporosis by age and treatment group, MEPS 1996-2004

HRGS male	GIOP state		1st Fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	0	-	0	-	-	-	-
31-50							
BP	2	6,236	0	-	-	-	-
CN	2	11,380	-	-	-	-	-
CT	0	-	0	-	-	-	-
51-70							
BP	2	17,164	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	3	23,438	0	-	-	-	-
71-90							
BP	2	33,701	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	2	23,981	0	-	-	-	-

Ave.=average; 1st Fracture=the first new events of osteoporotic fractures occurred after the treatment; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Wtd=weighted; Unwtd=unweighted.

§N=total number of subjects from 1996 to 2004.

*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.

**Rates per 1,000,000 person-years.

Table B.24 Incidence of repeated osteoporotic fracture in high-risk glucocorticoid male users with prior fracture by age and treatment group, MEPS 1996-2004

HRGS male	GIFX state		Repeated fracture			Incidence (/10^6)**	
Age (years) Treatment*	Unwtd N§	Wtd. N§	Unwtd N§	Wtd. N§	Ave. Age	1-year rate	3-month rate
11-30							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	4	31,412	0	-	-	-	-
31-50							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	8	131,442	0	-	-	-	-
51-70							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	17	230,752	2	12,714	65.3	55,098	14,069
71-90							
BP	0	-	0	-	-	-	-
CN	0	-	0	-	-	-	-
CT	10	117,745	0	-	-	-	-

Ave.=average; HRGS=high-risk users of glucocorticoid tablets at an accumulated prednisone-equivalent dose of 450 mg or more; MEPS=Medical Expenditure Panel Survey; Repeated fracture=the second new events of osteoporotic fractures occurred after the treatment; Wtd=weighted; Unwtd=unweighted.
§N=total number of subjects from 1996 to 2004.
*Treatment groups: BP=bisphosphonate group; CN=calcitonin group; CT=control group without using any anti-osteoporotic agent.
**Rates per 1,000,000 person-years.

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